DECLARATION OF RICHARD DAY

Certificate of Service

I hereby certify that this correspondence is being filed electronically with the U.S. Patent and Trademark Office *via* EFS-Web on June 11, 2009.

By: Michelle Baglio

Docket No.: 36672.6
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ian Alexander SHIELS et. al.

Application No.: 10/531,560 | Confirmation No.: 3534

Filed: 27 January 2006 | Art Unit: 1654

For: TREATMENT OF OSTEOARTHRITIS | Examiner: Christina BRADLEY

DECLARATION OF RICHARD DAY PURSUANT TO 37 C.F.R. 1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, **Richard Day**, declare as follows:

1. I am currently Professor of Clinical Pharmacology at the University of New South Wales located in New South Wales, Australia, a position I have held since 1990. I am also Director of Clinical Pharmacology & Toxicology at St Vincent's Hospital, located in Sydney. I have a clinical practice in Clinical Pharmacology, Rheumatology and Pathology at St Vincent's Hospital, located in Sydney.

2. The positions I have held and my scientific expertise have been previously stated in my First Declaration in respect of US application No 10/531,560 (This Application) dated 11 September 2008.

3. This is my Second Declaration in respect of This Application.

4. I have read the Final Office Action issued by the USPTO on this application on 11 December 2008. I understand that the Examiner, despite my previous declaration, considers that the use of the C5a receptor antagonists of This Application to treat osteoarthritis is obvious in light of a combination of Woodruff, Fairlie and Kivitz. From the Office Action I understand the examiner has principally maintained this objection due to the disclosure in Woodruff in the paragraph which bridges pages 2483 and 2484. With respect, in maintaining the rejection I believe Examiner Bradley has misinterpreted this passage of Woodruff.

5. The paragraph of Woodruff relied upon by Examiner Bradley is set out at point 15 of the Office Action. While it is clearly correct that this passage does mention osteoarthritis I do not believe the single mention of osteoarthritis in the first sentence of this paragraph would lead anyone of ordinary knowledge in the field of treatment of arthritis to believe that a C5a antagonist had any role as a possible therapeutic in osteoarthritis.

6. As discussed in detail in my previous declaration the Woodruff reference is focused on the use of a C5a antagonist in the treatment of rheumatoid arthritis. The model used in Woodruff was a model of an antigen-induced monoarticular Arthus reaction which produces a discrete lesion of highly reproducible severity in a single joint. This is a model of rheumatoid arthritis (p2483 2nd column). This is not a model for osteoarthritis.

7. Although both rheumatoid arthritis and osteoarthritis involve IL-1 induced cartilage destruction, the IL-1 production is initiated by different mechanisms. The animal models used to study rheumatoid arthritis and osteoarthritis are different. It is not possible to simply extrapolate from a rheumatoid arthritis model to an osteoarthritis model, just as it is not possible to simply extrapolate the effective treatment of symptoms of rheumatoid arthritis to the treatment of the underlying etiology of osteoarthritis, a position which I understand the Examiner has accepted.

Accordingly, I do not believe that a person working in the area of arthritis treatment would have seen the single reference to osteoarthritis in the paragraph bridging pages 2483 and 2484 of Woodruff to be suggesting in any way that a C5a antagonist would have a role in treating osteoarthritis.

8. The opening sentence of the paragraph of Woodruff relied upon by Examiner Bradley is the only mention of osteoarthritis in the Woodruff reference. This sentence reads:-

> "The destruction of cartilage in osteoarthritis results from the IL-1-stimulated degradation of proteoglycans and inhibition of chondrocyte proteoglycan synthesis (18)."

9. Reference 18 is a paper by Wim B van den Berg a copy of which is attached as Exhibit "A". This paper is cited as support for the statement made in relation to osteoarthritis. The van den Berg paper relates primarily to rheumatoid arthritis but does provide some discussion of the differences between osteoarthritis and rheumatoid arthritis in the final paragraph. In this paragraph it is stated that:-

> "Chondrocyte proteoglycan synthesis is suppressed in arthritis, but enhanced in OA." (*I understand the reference to arthritis to be rheumatoid arthritis and OA to be osteoarthritis*)

10. Firstly it is noted that as opposed to providing support for the statement in Woodruff regarding osteoarthritis van den Berg actually contradicts Woodruff as van den Berg states that chondrocyte proteoglycan synthesis is <u>enhanced</u> in osteoarthritis not inhibited as stated in Woodruff. Chondrocyte proteoglycan synthesis is inhibited in rheumatoid arthritis not osteoarthritis.

11. The remainder of the paragraph bridging pages 2483 and 2484 makes no mention of osteoarthritis. The paragraph ends with the following:-

> "In contrast, the C5a receptor antagonist used in this study significantly reduces the degree of structural pathology in the joint as well as other signs of the disease in rats. This ability to moderate structural changes in the joint is a clear advantage over most of the NSAIDs."

12. In my view this statement has nothing to do with the use of C5a antagonists in osteoarthritis. This passage is referring to the effects seen using a C5a antagonist in the model of rheumatoid arthritis used in Woodruff. As I have explained previously the models of rheumatoid arthritis and osteoarthritis are quite dissimilar and as such results obtained in the model of one disease can not be extrapolated to the other disease.

13. In my opinion the paragraph bridging pages 2483 and 2484 of Woodruff has little or nothing to do with osteoarthritis. In this regard I note that with the possible exception of the first sentence the remainder of the paragraph relates to rheumatoid arthritis. Copies of reference 17 & 34 referred to in this paragraph are attached as Exhibits "B" and "C" respectively. Both of these references are directed to rheumatoid arthritis and provide no information regarding osteoarthritis.

14. The emphasis on rheumatoid arthritis in this paragraph is not surprising as this is the thrust of the entire paper. In my opinion the fleeting reference to osteoarthritis in the paragraph bridging pages 2483 and 2484 would not have provided a person of ordinary skill in the field of treatment of arthritis with any information regarding the possible use of a C5a antagonist in the treatment of osteoarthritis. I believe that it is likely the person of ordinary skill would have simply ignored the reference to osteoarthritis as the paper does not provide any information regarding treatment of osteoarthritis or seen it is an error due to the mistaken reference to chondrocyte proteoglycan synthesis activity. In this regard it is possible that the reference to "osteoarthritis" should have been "rheumatoid arthritis" as this would clearly fit with

the remainder of the manuscript and the statement regarding chondrocyte proteoglycan synthesis activity.

15. In any case, given that the models for rheumatoid arthritis and osteoarthritis are different and that IL-1 induces cartilage destruction and the underlying mechanisms involved in IL-1 production in rheumatoid arthritis and osteoarthritis are believed to be different, I would not expect that a drug which reduces the degree of structural pathology in a model of rheumatoid arthritis to be effective in moderating structural changes in osteoarthritis. Accordingly, I would not expect that just because the C5a receptor antagonist AcF-[OPdChaWR] was shown by Woodruff to reduce the structural pathology in the joint of a rat model of rheumatoid arthritis, that it would be similarly effective in treating the chronic joint degeneration associated with osteoarthritis.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Dated:

2 June 2009

[Day, Month, Year]

By: Ric Day

Richard Day

EXHIBITS A - C

Certificate of Service

I hereby certify that this correspondence is being filed electronically with the U.S. Patent and Trademark Office *via* EFS-Web on June 11, 2009.

By: Michelle Boyle

Docket No.: 36672.6
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ian Alexander SHIELS et. al.

Application No.: 10/531,560 | Confirmation No.: 3534

Filed: 27 January 2006 | Art Unit: 1654

For: TREATMENT OF OSTEOARTHRITIS | Examiner: Christina BRADLEY

DECLARATION OF RICHARD DAY PURSUANT TO 37 C.F.R. 1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

This is **Exhibit A** referred to in the Declaration of **Richard Day**.

Impact of NSAID and Steroids on Cartilage Destruction in Murine Antigen Induced Arthritis

WIM B. van den BERG

W.B. van den Berg

Abstract. Cartilage destruction in arthritic joints is characterized by enhanced degradation of proteoglycans and inhibition of chondrocyte proteoglycan synthesis. This combination rapidly results in marked matrix depletion. Common nonsteroidal antiinflammatory drugs (NSAID) clearly suppress joint swelling and to some extent cellular infiltration, but do not protect against cartilage damage. In contrast, steroids given either orally or as a local depot preparation normalize chondrocyte proteoglycan synthesis. Similar effects can be reached using neutralizing antibodies against interleukin 1. (*J Rheumatol 1991*;(suppl 27)18:122–3)

Key Indexing Terms:
NSAID STEROIDS CARTILAGE DESTRUCTION ALLERGIC ARTHRITIS

Joint inflammation is accompanied by cartilage destruction, but the mechanism underlying destruction is still poorly understood. This complicates rational therapy. One approach is to block inflammation in general, in the hope of inhibiting the destructive process as well. A more selective approach would be to focus on the key mediator(s).

There is considerable debate on the role of granulocytes in cartilage destruction. There is no doubt that products of activated granulocytes, like elastase and oxygen metabolites have a high potency to degrade matrix proteoglycans and to inhibit chondrocyte synthetic function. However, recent data suggest that cartilage destruction proceeds undisturbed in antigen induced arthritis in neutropenic rabbits[1]. We have done similar experiments, comparing cartilage damage in 2 arthritis models in normal, neutropenic and elastase deficient (Beige) mice. Damage was markedly reduced in immune complex arthritis in neutropenic animals, pointing to a major role of granulocytes in this model. However, in the more complicated model of antigen induced arthritis, which is a T cell driven process, cartilage destruction was similar in Beige and normal mice[2], and was hardly less in neutrophenic animals. In particular, the variable of inhibition of chondrocyte proteoglycan synthesis was untouched. This means that there is substantial overkill by other mediators, probably from the inflamed synovial tissue. Most emphasis is now placed on the key role of interleukin 1 (IL-1).

We screened the potency of common nonsteroidal antiinflammatory drugs (NSAID), like piroxicam, diclofenac and tiaprofenic acid, in murine antigen induced arthritis. These drugs, when given from the onset of arthritis, clearly suppress edema formation as measured with Tc-uptake[3]. Slight effects were noted on cellular infiltration. The most marked protective effect was on osteophyte formation, piroxicam showing the highest potency[4]. Cartilage damage, in terms of proteoglycan loss and inhibition of chondrocyte proteoglycan synthesis, was unchanged, indicating that these drugs lack influence on a particular destructive process. Adverse effects, as noted for certain NSAID on osteoarthritic chondrocytes[5], were not seen on arthritic chondrocytes[4].

Steroids are protective, especially when given as an intraarticular depot preparation[4,7,8]. Osteophyte formation is markedly reduced and chondrocyte proteoglycan synthesis is normalized. This is illustrated in Figure 1. Steroids are given at Day 3 after arthritis induction, at a moment when the matrix is already depleted and chondrocyte synthetic function is severely suppressed. At Day 7 this is still the case in the control group, but not in the steroid groups. This observation becomes of even more relevance when we note that steroids, given in a normal joint, cause significant suppression of chondrocyte proteoglycan synthesis (40–50%), which can last for a number of weeks. Apparently, conditions in an arthritic joint are such that the chondrocytes are prone to shift to enhanced synthesis (to rebuild the depleted matrix), at the moment that the suppressive action of inflammatory mediators is abolished. It furthermore indicates that although steroids may have significant side effects, the overall effect on arthritic chondrocytes may be beneficial. This urges a reappraisal of careful steroid regimes in the treatment of rheumatic conditions.

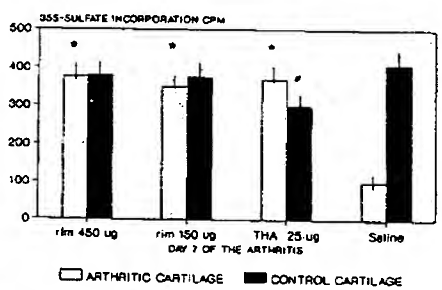

Fig. 1. Proteoglycan synthesis in patellar cartilage from normal (left) and arthritic (right) joints. This was measured *ex vivo* using radiolabelled sulfate incorporation in a 2 h culture period. Steroids (rimexolone and triamcinolone hexacetonide) (THA) were given by intraarticular injection at Day 3 after elicitation of murine mBSA induced arthritis. * $p < 0.002$ compared to the saline group (Student t). Also note the systemic effect of THA treatment on the left joint ($p<0.02$).

Steroids are potent inhibitors of IL-1 production. Moreover, there is no doubt that murine recombinant IL-1 can mimic events occurring in murine allergic arthritis, including the characteristic changes in arthritic cartilage[9]. To further underline the importance of IL-1, we treated arthritic mice with neutralizing anti-IL-1 antibodies (provided by Ivan Otterness). Such treatment prevented the suppression of chondrocyte proteoglycan synthesis (Figure 2), providing suggestive evidence that IL-1 is a key mediator in this process.

Comparison of joint destruction in experimental arthritis and osteoarthritis (OA) models reveals similarities and dissimilarities. Osteophytes are prominent in both models[10] and are sensitive to steroids and certain NSAID[4,8,11,12]. The mechanism of osteophyte formation is unknown, and may well be different in the 2 models, but is probably unrelated to IL-1. Chondrocyte proteoglycan synthesis is suppressed in arthritis, but enhanced in OA. The latter is hard to combine with a key role of IL-1, unless the enhanced synthesis is seen as a disregulated attempt at repair after previous IL-1 injury. Common NSAID are ineffective in preventing cartilage destruction in arthritis. In contrast, the NSAID tiaprofenic acid was shown to protect against cartilage destruction in OA, and could inhibit the impact of IL-1, at least *in vitro*. Perhaps the degree of inflammation and IL-1 production in arthritis is such that tiaprofenic acid is not strong enough. Part of the new drug development is focused on selective interference with IL-1. Careful examination of efficacy in the 2 models will yield further insight in the underlying mechanisms.

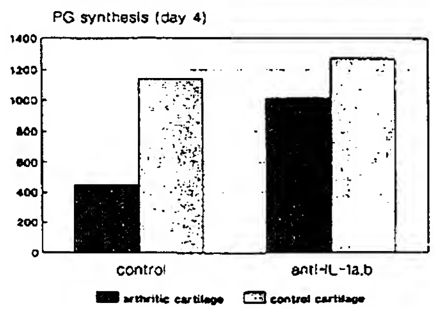

Fig. 2. Proteoglycan synthesis in patellar cartilage from normal (left) and arthritic (right) joints. Mice received 3 subcutaneous injections with 200 µl anti-IL-1a,b antiserum or control serum at Days −2, 0 and 2. Unilateral arthritis was induced at Day 0 by intraarticular injection of mBSA in preimmunized mice.

From the Department of Rheumatology, University Hospital Nijmegen, The Netherlands.
Wim B. van den Berg, PhD, Chief, Rheumatology Research Laboratory.
Address reprint requests to Dr. Wim B. van den Berg, Dept. of Rheumatology, University Hospital Nijmegen, 6525 GA Nijmegen, The Netherlands.

REFERENCES

1. Pettipher ER, Henderson B, Moncada S, Higgs GA: Leucocyte infiltration and cartilage proteoglycan loss in immune arthritis in the rabbit. *Br J Pharmacol 1988*;95:169–76.
2. Schalkwijk J, Joosten LAB, van den Berg WB, van de Putte LBA: Antigen induced arthritis in Beige (chediak-Higashi) mice. *Ann Rheum Dis 1990*;49:607–10.
3. de Vries BJ, van den Berg WB: Impact of NSAID on murine antigen induced arthritis. I. An investigation of antiinflammatory and chondroprotective effects. *J Rheumatol 1989*;(suppl 18)16:10–8.
4. de Vries BJ, van den Berg WB: Impact of NSAID on murine antigen induced arthritis. II. A light microscopic investigation of antiinflammatory and bone protective effects. *J Rheumatol 1990*;17:295–303.
5. Palmoski MJ, Brandt KD: Proteoglycan depletion, rather than fibrillation, determines the effects of salicylate and indomethacin on osteoarthritic cartilage. *Arthritis Rheum 1985*;28:548–53.
6. de Vries BJ, van den Berg WB, Vitters E, van de Putte LBA: Effects of NSAID on the metabolism of sulphated glycosaminoglycans in healthy and (post) arthritic murine articular cartilage. *Drugs 1988*;(suppl 1)35:24–32.
7. Hunneyball IM, Crossley MJ, Spowage M: Pharmacological studies on antigen induced arthritis in BALB/c mice I. *Agents Actions 1986*;18:384–93.
8. Joosten LAB, Helsen M, van den Berg WB: Protective effect of rimexolone on cartilage damage in arthritic mice: a comparative study with triamcinolone hexacetonide. *Agents Actions 1990*;(in press).
9. van de Loo AAJ, van den Berg WB: Effects of recombinant IL-1 on synovial joints in mice: measurement of patellar cartilage metabolism and joint inflammation. *Ann Rheum Dis 1990*;49:238–45.
10. van der Kraan PM, Vitters E, van de Putte LBA, van den Berg WB: Development of osteoarthritic lesions in mice by metabolic and mechanical alterations in the knee joints. *Am J Pathol 1989*;135:1001–14.
11. Williams JM, Brandt KD: Triamcinolone hexacetonide protects against fibrillation and osteophyte formation following chemically induced articular cartilage damage. *Arthritis Rheum 1985*;28:1267–74.
12. Pelletier JP, Martel-Pelletier J: Protective effects of corticosteroids on cartilage lesions and osteophyte formation in the Pond-Nuki dog model of osteoarthritis. *Arthritis Rheum 1989*;32:181–93.

Docket No.: 36672.6
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ian Alexander SHIELS et. al.

Application No.: 10/531,560

Confirmation No.: 3534

Filed: 27 January 2006

Art Unit: 1654

For: TREATMENT OF OSTEOARTHRITIS

Examiner: Christina BRADLEY

DECLARATION OF RICHARD DAY PURSUANT TO 37 C.F.R. 1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

This is **Exhibit B** referred to in the Declaration of **Richard Day**.

101. Boers M. Combination therapy in rheumatoid arthritis. Lancet 1999;354:952.
102. Hawley DJ, Wolfe F, Pincus T. Use of combination therapy in the routine care of patients with rheumatoid arthritis: Physician and patient surveys. Clin Exp Rheumatol 1999;17:S78-S82.
103. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. Lancet 1999;353:1568-73.
104. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996;334:1287-91.
105. Rau R. Combination DMARD treatment with parenteral gold and methotrexate. Clin Exp Rheumatol 1999;17:S83-S90.
106. Weinblatt ME. The role of current strategies in the future treatment of rheumatoid arthritis. Rheumatology 1999;38:19-23.
107. Breedveld FC. Future trends in the treatment of rheumatoid arthritis: cytokine targets. Rheumatology 1999;38:11-3.
108. Maini R, St. Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-9.
109. Moreland LW. Inhibitors of tumor necrosis factor for rheumatoid arthritis. J Rheumatol 1999;26:7-15.
110. Wolfe F, Pincus T. Data collection in the clinic. Rheum Dis Clin North Am 1995; 21:321-58.
111. Lanes SF, Lanza LL, Radensky PW, et al. Resource utilization and cost of care for rheumatoid arthritis and osteoarthritis in a managed care setting: the importance of drug and surgery costs. Arthritis Rheum 1997;40:1475-81.
112. Solomon DH, Bates DW, Panush RS, Katz JN. Costs, outcomes, and patient satisfaction by provider type for patients with rheumatic and musculoskeletal conditions: a critical review of the literature and proposed methodologic standards [see comments]. Ann Intern Med 1997;127:52-60.
113. Fries JF, Williams CA, Bloch DA. The relative toxicity of nonsteroidal antiinflammatory drugs. Arthritis Rheum 1991;34:1353-60.
114. Fries JF, Spitz PW, Mitchell DM, Roth SH, Wolfe F, Bloch DA. Impact of specific therapy upon rheumatoid arthritis. Arthritis Rheum 1986;29:620-7.
115. Fries JF, Williams CA, Bloch DA, Michel BA. Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models [see comments]. Am J Med 1991;91:213-22.
116. Wolfe F, Cathey MA. The effect of age on methotrexate efficacy and toxicity. J Rheumatol 1991;18:973-7.
117. Wilkieson CA, Madhok R, Hunter JA, Capell HA. Toleration, side-effects and efficacy of sulphasalazine in rheumatoid arthritis patients of different ages. Q J Med 1993;86:501-5.
118. Albers JM, Kuper HH, van Riel PL, et al. Socio-economic consequences of rheumatoid arthritis in the first years of the disease. Br J Rheumatol 1999;38:423-30.
119. Munro R, Hampson R, McEntegart A, Thomson EA, Madhok T, Capell H. Improved functional outcome in patients with early rheumatoid arthritis treated with intramuscular gold: results of a five year prospective study. Ann Rheum Dis 1998;57:88-93.
120. Stenger AAME, van Leeuwen MA, Houtman PM, et al. Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. Br J Rheumatol 1998; 37:1157-63.
121. van de Putte LBA, van Gestel AM, van Riel PLCM. Early treatment of rheumatoid arthritis: rationale, evidence, and implications. Ann Rheum Dis 1998;57:511-2.
122. Alarcon GS. Slow progression of joint damage in early rheumatoid arthritis treated with cyclosporin A or methotrexate [comment]. Arthritis Rheum 1997;40:791.
123. Van Gestel AM, Haagsma CJ, Furst DE, van Riel PLCM. Treatment of early rheumatoid arthritis patients with slow-acting anti-rheumatic drugs. Baillieres Clin Rheumatol 1997;11:65-82.
124. Dawes PT, Fowler PD. Treatment of early rheumatoid arthritis: A review of current and future concepts and therapy. Clin Exp Rheumatol 1995;13:381-94.
125. HERA Study Group. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA study. Am J Med 1995;98:156-68.
126. Felson DT, Anderson JJ, Meenan RF. Use of short-term efficacy/toxicity tradeoffs to select second-line drugs in rheumatoid arthritis. A metaanalysis of published clinical trials. Arthritis Rheum 1992;35:1117-25.
127. Fries JF, Williams CA, Ramey D, Bloch DA. The relative toxicity of disease-modifying antirheumatic drugs. Arthritis Rheum 1993;36:297-306.
128. Baker GL, Kahl LE, Zee BC, Stolzer BL, Agarwal AK, Medsger TA Jr. Malignancy following treatment of rheumatoid arthritis with cyclophosphamide. Long-term case-control follow-up study. Am J Med 1987;83:1-9.
129. Csuka M, Carrera GF, McCarty DJ. Treatment of intractable rheumatoid arthritis with combined cyclophosphamide, azathioprine, and hydroxychloroquine. A follow-up study. JAMA 1986;255:2315-9.
130. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Arch Intern Med 1999;159:2542-50.
131. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130:478-86.
132. Moreland LW. Inhibitors of tumor necrosis factor for rheumatoid arthritis. J Rheumatol 1999;26 Suppl 57:7-15.
133. Harriman G, Harper LK, Schaible TF. Summary of clinical trials in rheumatoid arthritis using infliximab, an anti-TNF-alpha treatment. Ann Rheum Dis 1999;58 Suppl 1:161-4.
134. Pincus T, Callahan LF. The 'side effects' of rheumatoid arthritis: joint destruction, disability and early mortality. Br J Rheumatol 1993;32 Suppl 1:28-37.
135. Kirwan JR, Russell AS. Systemic glucocorticoid treatment in rheumatoid arthritis — A debate. Scand J Rheumatol 1998; 27:247-51.
136. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose methotrexate on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol 1997;24:1489-94.
137. Cohen MD, Conn DL. Benefits of low-dose corticosteroids in rheumatoid arthritis. Bull Rheum Dis 1997;46:4-7.
138. Saag KG. Low-dose corticosteroid therapy in rheumatoid arthritis: Balancing the evidence. Am J Med 1997;103:31-9.
139. Kirwan JR, Byron M, Dieppe P, et al. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. N Engl J Med 1995;333:142-6.
140. Criswell LA, Such CL, Yelin EH. Differences in the use of second-line agents and prednisone for treatment of rheumatoid arthritis by rheumatologists and non-rheumatologists. J Rheumatol 1997;24:2283-90.
141. Gamez-Nava JI, Gonzalez Lopez L, Davis P, Suarez Almazor ME. Referral and diagnosis of common rheumatic diseases by primary care physicians. Br J Rheumatol 1998:37:1215-9.
142. Bolumar F, Ruiz MT, Hernandez I, Pascual E. Reliability of the diagnosis of rheumatic conditions at the primary health care level. J Rheumatol 1994;21:2344-8.

Management of Rheumatoid Arthritis: The Historical Context

LARRY W. MORELAND, ANTHONY S. RUSSELL, and HAROLD E. PAULUS

ABSTRACT. We review the historical highlights of the management of rheumatoid arthritis (RA). Studies of nonsteroidal antiinflammatory drugs, disease modifying antirheumatic drugs, and biological agents over 5 decades were evaluated and summarized. There is emphasis on drug therapy as it has developed and evolved from empirical relief of symptoms with salicylates to targeted intervention in the immunoinflammatory process with tumor necrosis factor inhibitors. A therapeutic paradigm has been proposed to rationalize the use of the available therapies. If one accepts the thesis that both the acute and chronic consequences of RA are due to persistent misdirected and inadequately controlled inflammation that causes tissue destruction and loss of function, then prolonged complete control of the abnormal inflammatory process is the fundamental first step in the management of all patients with RA. Unfortunately, even with the newest therapeutic options to treat RA, most patients achieve only partial suppression of inflammation and many lose therapeutic benefit after an initial good response. The management of persistent or recurrent rheumatoid inflammation and disability continues to be a challenge. It remains to be determined whether the future addition of more potent specific interventions in the immunoinflammatory process will be able to solve this problem without disarming host defenses against infections and tumors. (J Rheumatol 2001;28:1431–52)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — NONSTEROIDAL ANTIINFLAMMATORY DRUGS
TREATMENT — BIOLOGICAL AGENTS — DISEASE MODIFYING ANTIRHEUMATIC DRUGS

The ultimate goal of rheumatoid arthritis (RA) management is to restore the patient to normal non-RA status, asymptomatic, with normal physical, social, and emotional function and capacity to work, and with structurally and anatomically normal joints. Once achieved, this normalcy should be sustained without further medical intervention, i.e., the patient should have been "cured."

Even with the most optimistic scenarios, this goal could be attained only at the onset of RA before any irreversible joint or cartilage damage had occurred, or in those few fortunate patients whose arthritis does not cause structural damage. For the vast majority of patients who already exhibit evidence of joint erosions or cartilage damage, less perfect goals must be accepted. Since RA is a chronic disease that may begin any time between childhood and old age and usually persists for the entire remaining lifetime of the patient, it is evident that the specific aims of its management will vary among individual patients, depending on the aggressiveness of their disease, their age and life status at its onset, and their current life status as it is affected by the signs and symptoms of inflammation, decreased physical function, work disability, destruction of specific joints, and social and emotional coping capacity. A 25-year-old with recent onset RA who is incapacitated by the pain, stiffness, and exhaustion associated with uncontrolled inflammatory polyarthritis is very different from a 65-year-old with a 25 year history of RA who has been treated with a long list of antirheumatic therapies and is incapacitated by severely damaged or destroyed small joints of the hands and feet and a totally eroded hip joint. Thus, physicians who treat RA must be sensitive to the widely varying needs of the prevalent population of persons with RA and must be careful not to impose constraints that impede their therapeutic approach.

Nevertheless, if one accepts the thesis that both the acute and chronic consequences of RA are due to persistent misdirected and inadequately controlled inflammation that causes tissue destruction and loss of function, then prolonged complete control of the abnormal inflammatory process is the fundamental first step in the management of all patients with RA. Although the manifestations of acute inflammation, e.g., heat, redness, pain, swelling and loss of function, may become less obvious with time and symptomatic treatment, the progressive decline in functional capacity and increasing joint destruction demonstrated in longterm observational studies confirms the continued presence of inadequately controlled chronic inflammation[1-4]. Fortunately, controlled clinical trials have demonstrated that measurable

From the University of Alabama at Birmingham, Birmingham, Alabama, USA; the University of Alberta, Edmonton, Alberta, Canada; and the University of California at Los Angeles (UCLA), Los Angeles, California, USA.

Supported by an unrestricted educational grant from Centocor, Inc.

L.W. Moreland, MD, University of Alabama at Birmingham; A.S. Russell, MD, University of Alberta; H.E. Paulus, MD, UCLA.

Address reprint requests to Dr. L.W. Moreland, University of Alabama at Birmingham, 1717-6th Avenue South, SRC 068, Birmingham, AL 35294-7201. E-mail: larry.moreland@ccc.uab.edu

radiographic progression of joint damage can be moderated by leflunomide[5], methotrexate (MTX)[5], sulfasalazine[5], and infliximab[6] (compared to placebo in patients with well established RA of 5 to 15 years' duration), and with etanercept[7] and leflunomide[5] (compared to MTX in patients with relatively early RA of 1 to 5 years' duration). In all cases, improvement of signs, symptoms, and function also occurred.

Therefore, the universal basic goal in the treatment of all patients with RA is complete control of the abnormal inflammatory process. In the short term, this should be associated with major improvements in joint swelling, tenderness, stiffness, and mobility, and generalized improvement in energy and normalization of acute phase reactants. Longterm inflammation associated pain should improve, but pain (of a different character) related to structural damage may persist. The degree of feasible improvement in function will depend in a given patient on the relative contributions of reversible inflammation and irreversible structural damage to the dysfunction; where the latter is marked, the rate of progressive loss of function should slow and there may be some improvement, but substantial disability will persist. Similarly, progression of inflammatory damage to joints should stop, although in theory further damage may occur in joints that already have been distorted by prior structural damage. Intermediate goals of treatment may be similar to those expressed in the US Food and Drug Administration Guidance for Industry[8]: reduction of signs and symptoms, major clinical response, complete clinical response, remission, improvement in function/disability, prevention of structural damage.

We review historical highlights of the management of RA, emphasizing drug therapy as it has developed and evolved from empirical relief of symptoms with salicylates to specific intervention in the immunoinflammatory process with tumor necrosis factor (TNF) inhibitors, and discuss therapeutic paradigms that have been proposed to rationalize the use of the available therapies.

HISTORY OF RA TREATMENT

Nonsteroidal Antiinflammatory Drugs (NSAID)

NSAID reduce the signs and symptoms of established inflammation, but do not in themselves eliminate the underlying cause of the inflammation. Their effects on pain, swelling, heat, erythema, and loss of function begin promptly after their absorption into the blood and become fully evident within a few weeks. Drug withdrawal is quickly followed by exacerbation of signs and symptoms of inflammation. The drugs have no effect on the course of the basic disease process and do not protect against tissue or joint injury; thus, damage to joints continues to occur during the administration of nonsteroidal antiinflammatory agents to patients with chronic inflammatory arthritis.

Willow and poplar barks that contain salicin have been used since antiquity to treat pain, gout, and fever (Table 1). Soon after the isolation of salicylic acid from the bitter glycoside, salicin, in 1838, salicylic acid was noted to be an effective analgesic and antipyretic agent for the treatment of "acute and chronic rheumatism." Acetylsalicylic acid was first synthesized by Von Gerhardt, a French chemist, in 1853, but was not used therapeutically at the time. Sodium salicylate was introduced about 1860 in an effort to reduce the marked dyspepsia associated with salicylic acid. Its value in rheumatic fever was demonstrated in 1875. Aspirin was developed by Hoffman and Dresser in 1899 when a search for a salicylate preparation with reduced toxicity was undertaken[9,10]. An asymmetrical dose-response relationship with salicylates was recognized and very high doses were used to control the acute manifestations of rheumatic fever (6 g/day) and juvenile rheumatoid arthritis (JRA, 70 to 120 mg/kg/day)[11,12].

The term nonsteroidal antiinflammatory drug was first applied to phenylbutazone, which was introduced into clinical practice in 1949, three years after the dramatic demonstration of the antiinflammatory properties of the corticosteroids. Antipyrine, a forerunner of phenylbutazone, had been introduced in 1884, but fell into disuse when salicylates became more popular. A pharmacologic breakthrough occurred when indomethacin was selected by deliberate screening of numerous chemicals for activity against inflammation induced in rat paws by injection of carrageenan. Since the introduction of indomethacin in 1965, many other compounds have been found to suppress the acute development of rat paw edema following the injection of carrageenan or other irritating substances. Essentially all of the traditional NSAID were initially identified by their *in vivo* effects on this model of acute inflammation, and the model's ability to identify additional similar compounds seems limitless. Standard NSAID such as ibuprofen, fenoprofen, ketoprofen, flurbiprofen, naproxyn, diclofenac, tolmetin, piroxicam, and sulindac were selected by screening large numbers of chemicals with *in vivo* models of inflammation. Since these NSAID were selected because of their effect on induced acute inflammation in a whole animal model, it is apparent that they successfully moderate the general process of acute inflammation *in vivo*.

Various hypotheses have been advanced to explain the actions of NSAID. Under appropriate conditions, NSAID have been shown to uncouple oxidative phosphorylation, to displace an endogenous antiinflammatory peptide from plasma proteins, to inhibit lysosomal enzyme release, to inhibit complement activation, and to antagonize the generation or activity of kinins[13]. In 1971, Vane reported that aspirin and related compounds selectively inhibit the synthesis of prostaglandins[14] and proposed that the major toxic and therapeutic effects of NSAID might be accounted for by their ability to suppress the synthesis of prostaglandins by the enzyme cyclooxygenase. In 1990

Table 1. Historical highlights of NSAID therapy.

Introduced	Drug	Dose Range mg/day	Half-life (h)	GI Adverse Effects: Symptoms	GI Adverse Effects: Ulcers, Bleeds, Perforations, %/yr	Lethal Side Effects	Comments
Antiquity	Willow bark (salicin)	?	?	+++	?	?	For pain, fever, gout
1838	Salicylic acid	?	4–15	+++	?	?	
1860	Sodium salicylate	1500–6000	4–15	+++	?	Overdoses lethal	Rheumatic fever 1875
1899	Aspirin	1000–6000	4–15	+++	2–4	Overdose lethal, GI bleeding or perforation lethal	Platelet anticoagulant
1949	Phenylbutazone	200–800	40–80	++		Blood dyscrasia (16–22 deaths/million), Stevens-Johnson syndrome, Granulomatous hepatitis } occ. deaths	
1965	Indomethacin	50–200	3–11	+++			
1960s	Non-acetylated salicylates, enteric released aspirin	1500–5000	4–15	+ to ++		Overdose lethal	Better tolerated
1970s, 1980s	1st Generation NSAID					Overdose not lethal Estimate 7600 deaths per year in US from NSAID induced GI PUB	↑Liver toxicity with diclofenac Rare acute renal failure Rare anaphylaxis, aseptic meningitis, agranulocytosis, serious rashes
	Ibuprofen	1200–3000	2				
	Ketoprofen	100–400	2		PUB occur in 2–4% per patient-year of exposure		
	Diclofenac	75–150	1–2	++ to +++			
	Naproxen	250–1500	13				
	Sulindac	300–400	16				
	Tolmetin	800–1600	1				
	Piroxicam	20	30–86				
1990 to 1995	2nd Generation NSAID					Probably lower risk than 1st generation NSAID	Somewhat better tolerated than 1st generation NSAID, Nabumetone is a non-acidic prodrug with active acidic metabolite
	Etodolac	600–1200	7	+	2–4		
	Oxaprozine	600–1200	49–60	++	2–4		
	Nabumetone	750–2000	24	+	0.5		
1997 to 1998	COX-2 selective						Rofecoxib not approved for RA. Fluid retention with high doses
	Celecoxib	200–400	11	+	Probably < 1	Probably rare	
	Rofecoxib	12.5–25	17	+	Probably < 1	Probably rare	

PUB: perforation, ulcer and bleed.

Masferrer, *et al*[15] proposed that different pools of cyclooxygenase (COX) might be present, encoded by different genes. The complementary DNA (cDNA) of two isoenzymes, COX-1 and COX-2, and their respective messenger RNA (mRNA) were rapidly identified, cloned, and expressed in cultures of insect cell, making it possible to produce pure human COX-1 and COX-2[16]. These findings helped explain the linkage between the antiinflammatory benefits and the gastrointestinal (GI) adverse effects of the NSAID. Cyclooxygenase-1 (COX-1) is constitutively present in many tissues, and is responsible for the physiologic production of homeostatic and cytoprotective prostanoids in the gastric mucosa, endothelium, platelets, and kidney. Its inhibition is linked to many of the familiar adverse effects of NSAID. Cyclooxygenase-2 (COX-2) generally is not produced by unstimulated cells. Its production in leukocytes, vascular smooth muscle cells, human rheumatoid synoviocytes, and brain neurons is induced by stimuli such as mitogens, cytokines, and endotoxin, thus catalyzing the synthesis of proinflammatory prostaglandins. COX-2 is associated with carrageenan induced inflammation in experimental animals, certain aspects of inflammatory pain, and fever. In the brain, induction of COX-2 is associated with neurogenic pain and fever. COX-2 is induced during tissue repair and may be involved in healing of *Helicobacter pylori* associated peptic ulcers and mucosal damage in a rat model of colitis. COX-2 is physiologically involved in reproduction, i.e., the timing of ovulation and implantation of the blastocyst in the uterine wall. It is involved in bone remodeling and is induced in the renal macula densa and medullary interstitial cells during sodium restriction of rats[17]. COX-2 is also expressed in the podocytes of the

human glomerulus and the endothelial cells of renal arteries and veins, and is upregulated by inhibitors of angiotensin converting enzyme. Specific COX-2 inhibitors induce transient sodium retention without altering glomerular filtration rate[18].

To a considerable extent, the clinical properties and side effect profiles of NSAID are explained by their suppression of COX-1 and COX-2. Most NSAID inhibit COX-1 more efficiently than COX-2; COX-1 preferential NSAID include aspirin, indomethacin, ibuprofen, naproxyn, and piroxicam. Non-acetylated salicylates and diclofenac are about equal inhibitors of COX-1 and COX-2. Etodolac and meloxicam are COX-2 preferential by a ratio of about 10 to 1. Celecoxib and rofecoxib are COX-2 selective; the concentration required to inhibit COX-1 is about 1000 times greater than that required to inhibit COX-2[19].

Efficacy of NSAID. NSAID reduce the signs and symptoms of established inflammation. Amelioration of pain, swelling, heat, erythema, and loss of function begins promptly after their absorption into the blood and is rapidly reversible. Improvement of laboratory abnormalities, e.g., rheumatoid factor, acute phase reactants, serum albumin, hemoglobin, is not generally seen in clinical trials of NSAID therapy. Nevertheless, patients with RA who have symptoms of joint pain, tenderness, swelling, and stiffness during disease modifying antirheumatic drug (DMARD, e.g., MTX) therapy experience measurable benefit when adequate doses of an NSAID are added, and these symptoms promptly flare when the NSAID is withdrawn. This has been demonstrated in numerous NSAID clinical trials in which stable "background" treatment with a DMARD is continued, but the NSAID is shown to be more effective than control treatment with placebo.

NSAID clinical trials show more efficacy than is apparent in routine clinical practice because the baseline observations for the clinical trial are done during a required NSAID withdrawal flare of the signs and symptoms being measured. Patients who do not flare within a few days after stopping their pretrial NSAID are not admitted to the trial.

The maximum antiinflammatory potential of the various NSAID is about equal and is related to the duration of tissue exposure to effective concentrations of drug. Thus, higher doses and longer plasma half-life increase efficacy up to a point. For most NSAID, GI toxicity associated with COX-1 inhibition limits dosage. This is not the case with selective COX-2 inhibitors; nevertheless, with increasing doses, their efficacy reaches a plateau, and further increases in dose do not significantly increase antiinflammatory benefit. Thus, high doses of aspirin or indomethacin are as effective as the latest COX-2 selective drugs in the suppression of the symptoms of inflammation and fever.

In clinical use, the benefit of an NSAID is most evident during the post-withdrawal flare of joint pain, swelling, and stiffness that generally occurs within 5 or 6 half-lives after stopping an effective NSAID in an RA patient with active inflammatory disease. Resumption of the same or another NSAID rapidly reverses the flare, with statistically significant improvement within a few days to weeks. Patients adapt to the NSAID induced decrease in symptoms by increasing their physical activities as much as tolerated, until limited by increases in pain and stiffness. At this point, the benefit of the NSAID is no longer evident to the patient or physician, prompting a change to a different NSAID. Although clinical trials fail to document significant differences between NSAID if maximally effective doses are compared, individual patients frequently prefer one drug over others, perhaps due to better tolerability or efficacy in that individual at that time. Some NSAID, such as ketorolac, have been developed as analgesics, and others such as indomethacin and phenylbutazone are reputed to be more effective for spondyloarthropathies and gout. The scientific basis for these differences is not clear, but may relate to differences in drug metabolism or tissue penetration.

The efficacy of NSAID and DMARD should not be compared. Effective doses of an NSAID relieve many of the symptoms of inflammation without much effect on the underlying progression of the disease. An effective DMARD may completely suppress the disease progression, inducing a remission in some patients. Yet if a physician mistakenly stops an NSAID as soon as a slowly acting DMARD is started, the patient almost immediately notes increased pain, stiffness, swelling, and dysfunction, which is relieved by resumption of the NSAID. However, corticosteroid efficacy overlaps and surpasses that of NSAID. If one is willing to accept the adverse effect liability of corticosteroids, RA patients can and frequently are treated without NSAID.

Adverse effects. Toxicity has been a major problem with NSAID and since the 1800s development of new drugs has been driven by attempts to decrease their toxicity. Therapeutic or accidental overdoses of aspirin and salicylates (and acetaminophen) may be fatal, and frequently were encountered before the use of childproof caps and their displacement by safer NSAID. Phenylbutazone use was largely discontinued because of its association with aplastic anemia, agranulocytosis, and thrombocytopenia, with estimates of 16 to 22 deaths per million patients[13], and occasional deaths due to Stevens-Johnson syndrome or granulomatous hepatitis. Hepatic toxicity is fairly common; persistent abnormal transaminase values occurred in 5.4% of RA patients treated with aspirin and in 2.9% treated with other NSAID; it is more frequent with acetaminophen, diclofenac, sulindac, and phenylbutazone. COX-1 inhibition has been associated with decreased glomerular filtration rate and renal failure, especially in patients with marginal renal blood flow that is being supported by renal prostaglandins. The role of COX-2 in renal function is not as clear, but high doses of the specific COX-2 inhibitor rofecoxib have been associated with edema and transient decrease in urinary sodium excretion[13].

By far the most important adverse effects of NSAID are related to the suppression of COX-1 mediated gastroprotective prostaglandins, which suppress excess gastric acid secretion and help to maintain the gastric mucosal barrier, leading to NSAID related dyspepsia, epigastric pain, indigestion, heartburn, nausea, and vomiting. Loss of gastroprotection results in mucosal hyperemia, diffuse gastritis, superficial ulcers, and penetrating ulcers that may be associated with GI bleeding or perforations and sometimes death. By life table analysis of prospectively collected data from multiple NSAID submissions, the US Food and Drug Administration (FDA) estimates that GI ulcers, bleeding, and perforation occur in about 1 to 2% of patients who use NSAID for 3 months and about 2 to 4% of those who use them for one year. Based on ARAMIS (Arthritis, Rheumatism and Aging Medical Information System) data, Fries estimates that NSAID induced gastropathy is responsible for 76,000 hospitalizations and 7600 deaths each year in the United States[20].

Over the years, various strategies were used to try to improve the gastric tolerability of aspirin and the NSAID. Administration was recommended with food to dilute the direct gastric irritation. Aspirin was prepared in rapidly disintegrating tablets, enteric coated tablets, and timed release dosage forms with some decrease in gastric distress. Nabumetone is an inactive prodrug in the stomach; after absorption, it is rapidly metabolized to the active NSAID 6 MNA (6-methoxy-2-napthyl acetic acid). At first antacids, then H2 blockers, and finally proton pump inhibitors were used to decrease gastric acid. Then the synthetic prostaglandin misoprostol was developed to prevent the toxicity associated with NSAID induced suppression of gastric prostaglandins by replacing them with an orally administered exogenous prostaglandin analog. The Misoprostol Ulcer Complications Outcome Safety Assessment (MUCOSA) trial was designed to prospectively evaluate serious upper GI clinical events in a double blind, randomized, placebo controlled 6 month study of 8843 older patients with RA (> 52 yrs of age; mean age 68) in a protocol designed to reflect normal clinical practice[21]. All patients were taking one or more of 10 specified NSAID. None had active peptic ulcer disease or were taking antiulcer medications. During the 6 month study, 67 events occurred that were defined as definite serious events (i.e., bleeding, perforation, or obstruction): 25 serious upper GI events (0.5 percentage rate of complication) occurred in the 4404 patients taking misoprostol, 200 g 4 times a day, and 42 (0.95% rate of complication) occurred in the 4439 patients receiving placebo, a statistically significant difference ($p = 0.049$ by Fisher's exact test). Thus, the misoprostol group showed a 40% reduction in the rate of serious complications compared with the placebo group. The 0.95% rate of serious upper GI events during 6 months of NSAID treatment in the control group confirms the earlier 2% to 4% per year estimates of the FDA. Risk factors for NSAID associated upper GI tract complications in this prospective randomized clinical trial are similar to those found in case control and cohort studies: older age, previous peptic ulcer disease (odds ratio twice that of comparison patients), previous GI bleeding (2.5 times more common than in the comparison group), and history of cardiovascular disease (rate with cardiovascular disease history 1.84 times higher than in the comparison group). The rate of occurrence of symptomatic GI adverse events over the course of the MUCOSA trial was relatively uniform in both groups. Other suspected risk factors include concomitant corticosteroid use, degree of disability, and presence of comorbidity.

The cumulative risk of these serious events increases with the duration of therapy and is greater in patients with previous peptic ulcer disease. Fatal outcomes are more likely in elderly or debilitated patients. Higher dosages of NSAID probably entail greater risk than lower dosages. The patient's disease, age, and degree of inflammation need to be considered in determining the optimal dosage for each patient, and every attempt should be made to use the lowest dose that adequately controls the patient's symptoms.

The incidence of endoscopically determined gastric erosions or ulcers in prospective double blind controlled clinical trials with selective COX-2 inhibitors is similar to that with placebo and much less than that with naproxen or ibuprofen. However, there was no significant reduction in the incidence of symptoms of nausea, dyspepsia, or abdominal pain[17]. Thus, specific COX-2 inhibitors appear likely to markedly decrease the serious and potentially lethal GI complications of NSAID therapy, but may only marginally improve their GI tolerability, and seem unlikely to increase their efficacy. In addition, because COX-1 inhibition is required for platelet anticoagulation, specific COX-2 inhibitors cannot replace low dose aspirin prophylaxis for myocardial infarction or strokes. COX-2 is upregulated by direct lipopolysaccharide stimulation of brain microglial cells and may be important in the brain response to infection. It also seems to be necessary for embryo implantation in the uterine myometrium[18]. However, the potential adverse effects in brain or reproductive functions are unlikely to be more severe with specific COX-2 inhibitors than they have been with standard NSAID, which also inhibit COX-2. Nevertheless, displacement of traditional nonselective COX-1/COX-2 inhibitors has important public health implications and should reduce the risks of symptomatic treatment of RA.

Future improvements in the efficacy of NSAID-like symptomatic therapy for RA will probably require new approaches to the control of inflammation, such as inhibition of inducible nitric oxide synthase, inhibition of nuclear factor-kappa B, inhibition of MAP kinase (mitogen activated protein kinase), or other mediators of inflammation.

Disease Modifying Antirheumatic Drugs (including Biologicals)

Historical highlights of drug treatment for RA with DMARD and biological therapies are presented in Table 2. The major toxicities known to be associated with these therapies and "estimated" efficacy are listed for each agent.

Gold salts. Based on the benefits of aurothioglucose in the management of articular symptoms in patients with rheumatic fever and endocarditis, in 1927 there was a hypothesis that rheumatoid joint inflammation might be a manifestation of infection with mycobacteria, which at that time was thought to be suppressed by gold. Gold salts were subsequently used for treatment of RA and shown to be beneficial[22]. The clinical experiences with gold compounds over several decades resulted in acceptance of the utility of gold in the management of RA.

Although gold compounds have shown efficacy in RA[22-31], the mechanism(s) underlying their clinical efficacy remains to be established. The efficacy of gold compounds in the treatment of RA was first reported by Forestier, who noted benefit in over two-thirds of 550 patients he treated with gold salts[22]. Double blind studies later confirmed the efficacy of gold sodium thiomalate in the treatment of RA[23]. Serum rheumatoid factor titer, erythrocyte sedimentation rate, C-reactive protein levels, fibrinogen levels, circulating immune complexes, and levels of gamma globulin all have been shown to decrease significantly during treatment with gold compounds[24-26]. Some clinical studies suggest that progression of joint space narrowing and erosions is diminished during treatment with gold sodium thiomalate[27,28].

Unfortunately, a large percentage of patients with RA either continue to have manifestations of active disease despite 4 to 6 months of weekly chrysotherapy or, after initially responding to gold therapy, develop recrudescence of disease activity despite continued treatment[32,33].

Due to many factors, including lack of initial response to or subsequent escape from the initial beneficial effects of chrysotherapy, and significant numbers of patients who must discontinue treatment because of toxicity, only a minority of patients remain on gold treatment beyond 3 to 5 years[32,33]. Some longterm (5 year) outcome assessments indicate that chrysotherapy does not significantly influence the natural course of RA with regard to functional status and overall symptoms[34].

During the course of treatment with parenteral gold compounds, about 33% of patients experience adverse reactions (Table 2). Although many of these reactions are relatively mild and may require only temporary withholding of, or adjustments in, the dose of gold, severe mucocutaneous, bone marrow, or renal toxicity may require cessation of therapy. Less than 50% of patients treated with parenteral gold compounds continue gold after 5 years, with about 60% of treatment terminations attributable to toxicity[33].

Antimalarials. The first published use of antimalarial compounds for treatment of rheumatic diseases was in the 1890s for lupus rash. Observations concerning the beneficial effects of quinacrine in individuals with RA were first reported in 1951[35].

The early controlled trials with antimalarials showed suppression of joint inflammation in patients with RA treated with chloroquine[36-39] or with hydroxychloroquine[39-41]. Recent controlled, multicenter studies in patients with early RA[42] have shown a decrease in joint inflammation and stiffness with a low level of significant side effects. Antimalarial drugs also have been shown to be effective in decreasing joint inflammation in children with JRA[43].

The initial efficacy and lack of reported toxicity associated with antimalarial therapy in RA patients during the 1950–1960 period led to escalation of daily doses up to 10 to 15 mg/kg/day. While hydroxychloroquine is effective in the treatment of RA, its onset of action is generally slow, requiring 3-6 months to become effective[41,44]. To investigate the usefulness of hydroxychloroquine dose loading to increase the percentage of responders or rate of response in treating RA, a recent study was performed where RA patients with mild disease were randomized to receive either 400, 800, or 1200 mg/day for 6 weeks[45]. The degree of clinical response was increased in those patients who received the highest doses. Short term ocular toxicity was not dose related, although GI toxicity was dose related.

Retinal changes occur in patients with chloroquine and hydroxychloroquine[46,47]. A recent review of the ophthalmology literature supports the safety of hydroxychloroquine at a dose of 6 to 7 mg/kg/day in patients without renal failure[48]. Retinopathy was initially reported after use of chloroquine[49] and several retinopathy cases were reported in chloroquine treated patients, particularly in patients with discoid lupus erythematosus, with daily doses exceeding chloroquine 500 mg/day[50]. The retinopathy may persist or progress even after chloroquine has been discontinued[51].

Ocular toxicity with hydroxychloroquine was first reported in 1967[46]. From 1960 to 1989 a total of 18 cases of retinopathy in patients receiving hydroxychloroquine were reported either in the literature or to the FDA[48]; in 16 of 18 of these cases, the dose of hydroxychloroquine was greater than 7 mg/kg/day. The issue of cumulative dose toxicity with hydroxychloroquine remains controversial, but several reports indicate the risks are low[52]. Other ocular effects include corneal deposits that may cause haloes to appear around lights. These superficial corneal deposits are often linear-appearing streaks and are located below the pupil; they are reversible when the drug is discontinued, and do not progress to visual damage[53]. The corneal deposits are relatively infrequent in hydroxychloroquine treated patients. In high doses, antimalarial drugs can impair visual accommodation due to dysfunction of the ciliary body, a problem experienced as blurred vision[46].

Maculopapular rash may occur in 3 to 5% of patients

Table 2. Historical highlights of DMARD therapy.

Introduced	Drug/Biological	Toxicity Frequency	Toxicity Severity	Drug Related Mortality	Efficacy (1+ to 4+)
1935	Gold salts Gold sodium thiomalate Aurothioglucose	Mucocutaneous Renal (proteinuria) Myelosuppression Pneumonitis Polyneuropathy Nitritoid reactions Ocular or cutaneous chrysiases	Mild to severe	Yes	2+
1951	Antimalarials	Retinopathy (rare) Maculopapular rash (3–5%) Myopathy/cardiomyopathy Neuropathy (rare)	Mild to moderate	None	1+ to 2+
1960s	D-penicillamine	Mucocutaneous Renal Bone marrow suppression Hepatitis Pneumonitis Autoimmune disorder	Mild to severe	Yes	2+
1970s	Sulfasalazine	Mucocutaneous Hematologic Pneumonitis Drug induced SLE	Mild to moderate	Rare	1+ to 2+
1970s	Azathioprine and Cyclophosphamide	Myelosuppression Gastrointestinal Hepatotoxicity Pneumonitis Rash Congenital deformities Malignancy Infections	Mild to severe	Uncommon	2+
1980s	Auranofin	Same as injectable but less frequent	Mild to severe	Rare	1+
1980s	Methotrexate	Stomatitis Hepatotoxicity Lung-fibrosis, pneumonitis Lung-pneumonitis Hematopoietic-cytopenia Abortifacient, teratogenic Infections-opportunistic (rare) CNS toxicity Alopecia, rash Neoplasia-?	Mild to severe	Uncommon	3+
1990s	Cyclosporine	Nephrotoxicity Hypertension Hirsutism	Mild to severe	Uncommon	2+
1998	Leflunomide	Diarrhea Rash Alopecia Elevated liver enzymes Teratogenic	Mild to severe	Rare	3+
1998	Etanercept	Injection site reactions (37%), infections	Mild	Rare	4+
1999	Infliximab	Antibody responses to murine protein, infections	Mild	Rare	4+

receiving antimalarial medications. Patients taking longterm chloroquine and hydroxychloroquine may develop areas of hyperpigmentation in photo exposed regions. Muscle weakness and vacuolization of muscle cells on biopsy have been reported in patients receiving chloroquine[54]. A few cases of cardiomyopathy have been reported in chloroquine treated

patients[55-57]. Leukopenia and aplastic anemia have developed during antimalarial treatment with both chloroquine and hydrochloroquine, but the relationship to drug treatment remains unclear[58-60].

Many mechanisms have been proposed for modulation of the immune response by antimalarial drugs. One attractive mechanism is that antimalarials interfere with the "presentation of antigen" by macrophages to T cells[61]. Additional mechanisms of action for antimalarials have been proposed including inhibition of DNA polymerase[62] and interference with phospholipase A1[63], interference with neutrophil superoxide release[64], and inhibition of cytokine release [including interleukin 1 (IL-1), tumor necrosis factor (TNF), interferon-γ] has been reported with chloroquine and hydroxychloroquine[65-67]. These activities would be expected to result in a rapid onset of antiinflammatory activity (i.e., similar to corticosteroids or NSAID), but the clinical onset of benefit with antimalarial drugs takes several months after starting medication.

D-Penicillamine. Penicillamine was first identified in acid hydrolysates of penicillin[68]. The potential effectiveness of penicillamine in disrupting disulfide bonds in IgM rheumatoid factors provided the initial rationale for its use in rheumatoid arthritis[69]. Improvement in synovitis and other disease manifestations was documented during clinical trials with the drug in the 1960s and early 1970s.

In controlled clinical trials, penicillamine has been found to be as effective as gold and azathioprine in the treatment of RA[70-72]. Since the dose must be increased gradually, clinical responses may not become apparent for several months after institution of therapy.

Treatment with penicillamine is usually initiated with an oral daily dose of 250 mg. The daily dose is gradually increased in 125 to 250 mg increments every 8 to 10 weeks. If the desired clinical effect has not been achieved after 6 months of treatment with this dose, gradual increases in the dose up to 1000 mg daily may benefit some patients[73,74].

Side effects observed in patients treated with D-penicillamine include mucocutaneous, hematologic, and renal toxicity and are often a limiting factor when using penicillamine in the treatment of RA (Table 2). Cutaneous reactions are the most common side effects experienced during treatment with penicillamine. In patients with RA, therapy with penicillamine is associated with a greater than expected occurrence of a variety of autoimmune syndromes. These include polymyositis, myasthenia gravis, pemphigus, and systemic lupus erythematosus.

Cytotoxic drugs (azathioprine and cyclophosphamide). Although commonly referred to as a cytotoxic drug, azathioprine also exerts antiproliferative, immunoregulatory, and antiinflammatory actions that may play as important roles as the cytotoxic effects in treating RA.

Controlled trials have documented the effectiveness of azathioprine in RA[75-77], and longterm followup studies confirmed continued clinical benefit[78-81]. Comparisons of azathioprine and MTX in patients with RA have produced conflicting results[82-86]. A retrospective study and one prospective controlled trial comparing azathioprine and MTX suggested that MTX was superior to azathioprine[83]. Three other prospective randomized trials, however, have not revealed a difference in efficacy between the two drugs[84-86].

Several adverse effects have been associated with azathioprine (Table 2). Adverse drug effects caused discontinuation of azathioprine in 19 to 32% of patients[87-90].

Nitrogen mustard was the first alkylating agent used in the treatment of refractory RA in 1951[91]. Cyclophosphamide has since become the principal alkylating agent used to treat rheumatic diseases. Although efficacious, the alkylating agents exhibit serious longterm toxicity, especially the induction of malignancies, which is a major concern. Cyclophosphamide and chlorambucil are not approved by the FDA for the treatment of RA. Several uncontrolled[92-96] and controlled trials have evaluated cyclophosphamide therapy in patients with RA. The daily dose of cyclophosphamide used in RA is generally 1 to 2 mg/kg. In view of their carcinogenicity, alkylating agents are now rarely used to treat RA.

Alkylating agents exhibit significant associated toxicities that must be considered in the risk-benefit assessment and reviewed with each patient before treatment is considered (Table 2). Monitoring is essential to minimize adverse effects in patients receiving these drugs.

Sulfasalazine. Sulfasalazine was initially developed specifically for the treatment of RA. In the late 1930s, Svartz designed a compound that contained both a salicylate and a sulfa component, and, in early 1942, reported positive therapeutic benefits of salazopyrin (sulfasalazine) in rheumatic polyarthritis and ulcerative colitis. In 1949, Sinclair and Duthie[97] published an uncontrolled trial comparing gold, sulfasalazine, and placebo. However, no significant differences were reported in any group. The results of this study were widely accepted for the next 30 years, and investigation into the efficacy of sulfasalazine in RA did not progress until the reports from McConkey, *et al* suggested beneficial effects with sulfasalazine in RA[98,99]. Since then several controlled clinical trials have also suggested efficacy in RA[100-103]. Although sulfasalazine has been used as therapy for RA for almost 50 years, its mechanism of action remains undefined.

About 30% of patients treated longterm with sulfasalazine discontinue the drug because of adverse effects. The adverse reactions associated with sulfasalazine are usually benign and readily reversible with discontinuation of the medication. The adverse effects associated with sulfasalazine can be divided into two major categories. The first is dose related and acetylator phenotype dependent. These effects include nausea, vomiting, headache, malaise, hemolytic anemia, reticulocytosis, and methemoglobinemia[101]. The second group of adverse events appears as a hypersensitivity reaction and includes rash, aplastic anemia, and autoimmune hemolysis (Table 2).

Methotrexate. Aminopterin, a folic acid analog and precursor of MTX, was first reported as being used for the treatment of RA by Gubner in 1951[104]. Over the next few years dermatologists investigated the use of MTX and demonstrated its efficacy for manifestations of psoriasis[105]. In the 1980s randomized clinical trials for RA were conducted[106-109] and MTX was approved by the FDA as a DMARD for the treatment of this disease in 1987[110].

The exact mechanism of action of MTX in improving the clinical manifestations of RA is not completely understood. MTX is capable of inhibition of folic acid-dependent pathways. In addition, MTX affects several mediators of inflammation, which likely explains the rapid clinical response observed in patients treated with this agent. These include IL-1[111,112], IL-6[113], leukotriene B4[114,115], and phospholipase A_2 activity[116]. MTX also has been shown to have immunosuppressive effects[117-119].

MTX is currently the most commonly used therapeutic agent for RA. Several randomized, placebo controlled clinical trials were conducted in the 1980s demonstrating its short term clinical benefits[106-109]. The longterm efficacy of MTX in RA has been established by several investigators[120-130]. After 5 years, MTX treated patients with RA exhibited about a 50% probability of still receiving MTX, compared to 15 to 20% for other DMARD such as gold salts or D-penicillamine[129]. It has been noted that the drug survival curves suggested that patients who began taking MTX early in the 1980s had a lower probability of continuing MTX than those patients who had started it in the late 1980s, possibly related to the growing experience of both patients and physicians with its use[129,131].

Until recently prevention of disease progression by MTX had not been definitely determined radiographically[132-134]. The recently published placebo-controlled trial comparing MTX to leflunomide showed that both these drugs were superior to placebo in slowing radiographic progression of disease in a relatively early onset RA patient population[5,135].

Adverse events reported with MTX therapy in RA vary in severity from minor to severe (Table 2). GI manifestations have been reported to occur in as many as 60% of MTX treated RA patients[136]. Many GI manifestations can be alleviated by the concomitant administration of folic acid, or a change in route of administration (from oral to parenteral). The occurrence of liver damage after prolonged administration of MTX for RA was a matter of serious concern in the 1980s based on previous experience with the drug in the treatment of psoriasis[137-144]. It has now become evident that clinically significant liver disease is less frequent than previously predicted. The potential toxicities of MTX in the treatment of RA patients has resulted in the American College of Rheumatology (ACR) developing guidelines for monitoring for some of these events[145].

An acute pulmonary syndrome or allergic pneumonitis, although uncommon, is a potentially severe and fatal adverse event[146-153]. Infectious processes need to be ruled out in this clinical setting.

Longterm observational studies with the use of MTX in RA patients have revealed an acceptable toxicity profile as well as sustained clinical benefit. However, few data are available regarding the effect of MTX on mortality in RA. Recent data suggest that MTX therapy may improve life expectancy even in patients with advanced RA[154].

Leflunomide. Leflunomide was recently approved (1998) for the treatment of RA. Three pivotal clinical trials have been performed within the past few years. A phase III study conducted in the United States and Canada included 482 MTX naive adults with active RA[135]. Patients received either leflunomide (20 mg/day), MTX (7.0-15.0 mg/wk), or placebo for 52 weeks. Leflunomide was statistically equivalent to MTX in relieving the signs and symptoms of active RA.

Another study was conducted in 358 sulfasalazine naïve adults with active RA comparing leflunomide (20 mg/day), sulfasalazine (2 g/day), or placebo[155]. Leflunomide was equivalent to sulfasalazine in improving signs and symptoms of RA. A third study was conducted in Europe, Australia, and New Zealand, where 999 MTX naïve adults with active RA were randomized to receive leflunomide (10 mg/day) or MTX (7.5–15.0 mg/wk) for 52 weeks[156]. In this study MTX was superior to leflunomide in improving RA signs and symptoms.

In these 3 studies, leflunomide, MTX, and sulfasalazine were all statistically better than placebo in slowing disease progression measured radiographically. Leflunomide, MTX, and sulfasalazine were not statistically different from each other in mean changes in total scores[5].

In an open label trial of leflunomide and MTX combination treatment, 30 patients with RA were treated for 52 weeks[157]. Sixteen (53%) of the patients met the ACR criteria for a 20% improvement in symptoms. Of concern, a 10% incidence of transaminase elevations was observed. A randomized, placebo-controlled combination trial is currently in progress to better define the tolerability of this combination.

Adverse events considered related to leflunomide in the controlled trials included diarrhea, rash, reversible alopecia, and liver transaminase elevations (Table 2). Pregnancy is contraindicated with leflunomide and MTX because both are teratogenic. Additional clinical studies are needed to determine if extended treatment with leflunomide causes liver damage.

Cyclosporine. Cyclosporine has been the most extensively investigated of the immunomodulatory agents. Cyclosporine has variable antifungal properties, but was devel-

oped primarily because of its potent immunosuppressive properties[158,159]. Most of its effects on immune responses are secondary to relatively selective inhibition of T cell activation[160,161]. Cyclosporine forms complexes with cytoplasmic binding proteins, called immunophilins, which appear to be essential in exerting the immunosuppressive effects.

The first study of cyclosporine as a treatment for RA was reported by Herrmann and Mueller in 1979[162]. This initial open label evaluation of what would now be considered very high doses of cyclosporine was performed in 7 patients with RA. Elevations of serum creatinine and the development of herpes zoster in 2 patients slowed the development of this agent for treating RA. Other open label trials in RA were initiated in the early to mid-1980s[163-168]. While clinical efficacy was noted, again elevations of serum creatinine levels were of major concern. Multiple controlled trials evaluating cyclosporine in RA have now been performed[169-176]. A majority of patients with RA treated with cyclosporine in clinical trials had average disease durations of over 10 years and had previously received 3 or more slow acting antirheumatic drugs.

The toxicities of cyclosporine include reversible and irreversible renal disease, hypertension, and hirsutism.

Combination DMARD. Only a few years ago combination DMARD therapy was regarded as an unusual approach to patients with RA, and was generally a treatment for patients with the most severe disease[177-179]. However, in 2000 almost all rheumatologists use combination DMARD therapy in some patients[180,181]. This shift in the treatment paradigm for RA may be explained in part by a more accurate description of the natural history of RA, availability of improved DMARD (i.e., MTX), and recognition that partial control of inflammation likely does not prevent joint damage.

DMARD were once referred to as "remission-inducing," a term that should no longer be used, as sustained remission is seen in fewer than 2% of patients treated with traditional DMARD monotherapy[182]. However, continuous treatment with DMARD does ameliorate the course of RA[183-186], including retardation of radiographic progression[187-189]. Over the past 10 years several new DMARD have become available, including cyclosporin A, leflunomide, etanercept, and infliximab, all of which have been studied as monotherapy and in combination with MTX. MTX emerged as a major advance during the 1990s, with longterm effectiveness. Although MTX is continued for over 5 years by more than 50% of patients[190,191], few patients with RA are in complete remission, and many, if not most, may be candidates for combination therapy.

MTX is the most commonly used "anchor drug" in combination therapy. Evidence from randomized, controlled clinical trials and observational studies has indicated increased efficacy and acceptable (and often lower) toxicity for combinations of MTX plus cyclosporine, hydroxychloroquine, sulfasalazine, leflunomide, etanercept, and/or infliximab. Further studies lasting 5 years or more are needed to determine the longterm effectiveness, toxicities, and optimal clinical use of disease modifying antirheumatic drug combinations.

Early uncontrolled clinical studies suggested that combination therapy with DMARD was efficacious[178,192]. However, initial randomized controlled clinical trials yielded varying results, with some suggesting no advantages to combination therapy[194-198]. The conflicting conclusions of these early studies may partly reflect design issues in clinical trials, such as patient selection, short time frame, and use of surrogate markers, all of which may limit recognition of differences between various regimens despite inclusion of control groups. Over the past 5 years, several randomized, controlled clinical trials with more complex designs have indicated that combinations of MTX with other DMARD are more effective than single agents, with acceptable toxicities (Table 3).

It seems unlikely that one particular combination of DMARD will be best for all patients, and some patients will respond sufficiently to monotherapy and will not require combination therapy. Although more patients respond to MTX than to any other drug, certain patients cannot tolerate MTX and other patients may respond more to other available drugs.

Anti-TNF agents. An important advance in treatment of RA is the advancement of therapies targeted at specific inflammatory processes involved in the disease. Etanercept, a TNF inhibitor, was the first biological agent approved for the treatment of RA (November 1998). Infliximab, a chimeric (mouse/human) anti-TNF monoclonal antibody (Mab), was also approved by the FDA for use in the treatment of RA in November 1999.

The TNF precursor is found in a variety of cells throughout the body. Macrophages appear to be the primary site of TNF production in RA with the active form of TNF, via TNF-α converting enzyme (TACE) mediated cleavage of the precursor molecule. After being shed from the cell surface, these soluble TNF molecules aggregate into trimolecular complexes that subsequently bind receptors found on a variety of cells, including fibroblasts, leukocytes, and endothelial cells. Two TNF receptors have been described, the p55 (also called p60) receptor and the p75 (also called p80) receptor.

TACE also cleaves the extracellular domain of the cell bound TNF receptors, forming soluble TNF receptors (sTNFR). These circulating sTNFR are then free to bind the trimolecular TNF complexes, rendering them biologically inactive; thus, the sTNFR function as natural inhibitors of TNF mediated inflammation.

A variety of physiological functions have been ascribed to TNF-TNF receptor interactions. TNF blocks the action of lipoprotein lipase, causing severe cachexia in experimental models of chronic infection. Additionally, TNF induces programmed cell death (apoptosis) and stimulates the release of several proinflammatory cytokines, including IL-6, IL-8, and IL-1. TNF also induces the release of matrix metalloproteinases from fibroblasts, chondrocytes, and neutrophils, and upregulates the expression of endothelial adhesion molecules, leading to the migration of leukocytes into extravascular tissues.

Table 3. Recent clinical trials of combination therapy with 2 or more disease modifying antirheumatic drugs in RA that indicate greater efficacy of combination therapy*.

Study, Year	Patients	Therapy Compared
Tugwell, 1995[226]	148	MTX plus cyclosporine**; MTX only
O'Dell, 1996[222,226]	102	MTX plus sulfasalazine plus hydroxychloroquine; sulfasalazine plus hydroxychloroquine, MTX only
Boers, 1997[136]	155	Sulfasalazine plus MTX plus prednisolone; sulfasalazine only (may be replaced by MTX after 6 months)
Maini, 1999[231]	428	Infliximab** plus MTX; MTX plus placebo
Maini, 1998[200]	101	Infliximab plus MTX; infliximab only; MTX only
Weinblatt, 1999[203]	89	MTX plus etanercept**; MTX plus placebo
Mottonen, 1999[232]	199	MTX plus sulfasalazine plus hydroxychloroquine plus prednisolone; sulfasalazine

*Modified from reference[227].
**Added in patients who tolerated MTX but had inadequate benefit.
MTX: methotrexate.

Etanercept. Etanercept is a recombinant, soluble TNF receptor (p75) fused to the Fc portion of a human IgG1 molecule. Fusion to an Fc fragment gives the agent several advantages over unconjugated soluble receptors. The dimeric construct results in significantly longer serum half-life, increasing the binding affinity for the trimolecular TNF aggregate. Etanercept's mode of action relies on its ability to bind TNF in serum, rendering the cytokine biologically inactive. The serum half-life of etanercept is 3–4 days.

Etanercept has proven to be a potent DMARD with a favorable toxicity profile[7,199-205]. A phase II, double blind, placebo controlled 3 month trial[201] randomized 180 patients with active, longstanding RA to 1 or 3 doses of etanercept (0.25, 2, or 16 mg/m^2) or placebo, all given by subcutaneous (sc) injection twice weekly. High dose (15 mg/m^2) etanercept was superior to both the low doses and placebo. Using standard ACR criteria[206] to evaluate the treatment response, 75% of patients receiving etanercept 16 mg/m^2 experienced 20% improvement at trial end, the majority showing substantial benefit as early as 1 month into the study. Etanercept injections were associated with minimal toxicity; minor injection site reactions were the only observed adverse effect seen more commonly in the etanercept groups versus placebo.

The phase III trial[202] differed from the phase II trial both in terms of dosing and duration of the investigation. In this 6 month, double blind, placebo controlled trial, investigators compared fixed doses (10 mg and 25 mg sc twice a week) with placebo. Again, the high dose regimen resulted in substantial clinical benefit with little associated toxicity. Patients receiving etanercept experienced sustained rapid benefit, often within the first month of therapy. Fifty-nine percent of patients met ACR criteria for 20% improvement (ACR 20). Forty percent met similar criteria for 50% improvement. Functional activity, measured by the Health Assessment Questionnaire (HAQ), showed significant improvement over the course of the study. In terms of the disability index, patients receiving placebo had a mean change from baseline of 2%, compared with 39% for those in the etanercept 25 mg group. Again, transient injection site reactions remained the most commonly observed adverse event in the etanercept groups compared with placebo. In all of the controlled trials, injection site reactions were seen in 37% of those receiving etanercept versus 10% of those receiving placebo ($p < 0.05$).

Data on the longterm use of etanercept has been presented at the ACR national meetings[205]. A large cohort of patients (N = 713) receiving etanercept with a cumulative exposure to drug of 1152 patient-years was followed longitudinally. The clinical benefit seen in previous short term clinical trials was maintained in longterm followup. There was no increase in serious toxicity over the course of the study. Minor injection site reactions, resulting in study withdrawal by less than 0.5% of patients, were the most common adverse event.

Data from this longterm study begins to address some of the concerns about the general effects of blocking TNF activity. Specifically, there was no increase in infectious requiring intravenous antibiotics. Longterm followup

revealed no increase in the incidence of any infection compared with placebo controlled studies. There were 9 reported cases of incident neoplasia, less than the expected number (10.7) calculated from the NCI SEER (National Cancer Institute Surveillance, Epidemiology and End Results) database. No patients have developed drug induced lupus or anticardiolipin antibody syndrome while receiving etanercept.

The use of etanercept in combination with MTX for the treatment of longstanding refractory RA has been studied[203]. Patients with active disease despite an average of 18.3 mg/wk of MTX were randomized to receive either etanercept (25 mg sc twice a week) or placebo. The addition of etanercept to MTX resulted in substantial benefit. At the end of the 24 week trial, 71% of those receiving combination therapy met ACR 20 criteria, compared with 27% of those receiving placebo plus MTX. The combination resulted in significantly greater improvement in all individual measures of disease activity used to define improvement by the ACR method. Minor injection site reactions were the only adverse event reported more often in the MTX-etanercept group.

Currently, etanercept is approved for use in RA patients who have not improved with 1 or more DMARD. While the majority of studies have been in patients with longstanding DMARD refractory disease, there is accumulating evidence that etanercept will slow disease progression when given earlier in the disease course. Results from the ERA (the Use of Etanercept in Early RA) trial were published[7].

The ERA trial included 632 patients with early RA (disease duration < 3 years) assigned to 1 of 3 treatment arms: (1) etanercept 25 mg twice a week and placebo oral tablets once a week, (2) etanercept 10 mg and placebo tablets, or (3) MTX 7.5 initially, rapidly increased to 20 mg and placebo injections. All patients received 1 mg folic acid daily, to reduce the dose limiting toxicity of MTX. The trial duration was 1 year, and the data was assessed using intent-to-treat analysis. The MTX dose was rapidly escalated in the first 8 weeks of the trial in order to optimize its effect, and an average dose of 18.3 mg/wk was achieved. Baseline characteristics of the study groups, including measures of disease activity, were similar.

Radiographic evidence of joint damage was measured by a modified Sharp score, including components for both joint space narrowing and erosions. At the end of the trial, there were no statistically significant differences in radiographic progression between Sharp total scores for etanercept and MTX. However, when examining the results by individual component scores, etanercept (25 mg) was more effective than either low dose etanercept or MTX at reducing the progression of joint erosions. This difference was statistically significant. Seventy-five (75%) of the patients in the etanercept 25 mg group had no erosions, versus 57% of the MTX group ($p < 0.001$).

In the ERA trial clinical efficacy was assessed by the area under the curve (AUC) calculated from a numeric ACR (ACR-N) response. The ACR-N represents the actual percentage of improvement in ACR criteria for an individual patient. The AUC for etanercept was significantly superior to that for MTX at both 6 months and 12 months ($p = 0.002$ and $p = 0.009$, respectively).

Study withdrawals related to toxicity were more common among those receiving MTX, while infection rates were lower in those receiving etanercept. Of patients receiving MTX (n = 217), 10 withdrew secondary to adverse events, compared with 5 of 207 receiving etanercept 25 mg. Laboratory abnormalities were similar among the 3 cohorts, with the exception of elevated liver function tests and lymphopenia, which were more frequent in the MTX group. About twice as many patients taking MTX as patients taking etanercept (both dose groups) had elevations of SGOT (32% vs 16%) or SGPT (44% vs 23%). Minor injection site reactions were the most commonly observed adverse event for patients receiving etanercept (37% of those receiving 25 mg of etanercept experienced these reactions, vs 7% of those receiving MTX).

Infliximab. Infliximab is a chimeric (murine/human construct) anti-TNF Mab composed of a constant region from human immunoglobulin and a variable region from murine immunoglobulin. Previously approved for the treatment of Crohn's disease, infliximab received FDA approval for the treatment of RA in November 1999. Clinical trials summarized below have confirmed both the efficacy and tolerability of the agent when used in patients with DMARD refractory RA, both alone and in combination with MTX[6,207-210].

In the initial phase I, open label trial, Elliott and colleagues[210] studied the use of infliximab in 20 patients with active, longstanding RA. Patients had a median disease duration of 10.5 years and had failed a median of 4 previous DMARD. Patients received a total of 20 mg/kg of intravenous infliximab given in divided doses over the course of 12–14 days. Clinical response to the treatment was substantial. Morning stiffness decreased from a median of 180 minutes at study entry to a median of 5 minutes at week 6. Pain scores decreased from 7.1 to 1.9 (range 0–10) over the same time period, representing an improvement of 73%. Swollen joint count dropped from 18 to 5, while serum C-reactive protein (CRP) levels fell from a median 39.5 mg/dl at study entry to 8 mg/dl at week 6. Functional capacity, as measured by HAQ score, improved significantly from a median of 2.0 at study entry to 1.1 by 6 weeks. Patients showed sustained benefit following the last dose of infliximab, with response duration ranging from 8 to 25 weeks (median of 14).

A phase II placebo controlled trial[207] included 73 patients who, similar to those in the phase I trial, had longstanding DMARD refractory RA. Results in this trial were similar. Patients in the active treatment groups received only a single intravenous infusion of infliximab, either 1 mg/kg or 10 mg/kg. At the 4 week assessment, 79% of patients receiving 10 mg/kg reported at least 20% improvement in symptoms and half had at least 50% improvement in disease activity.

In both the phase I and phase II trials, infliximab was well tolerated without reports of any clinically significant adverse events. No patients had evidence of human antichimeric antibodies (HACA) subsequent to infliximab administration when assessed at the 4 week examination[210].

In a continuation of this phase II trial[208], 8 of the original 20 patients from the phase I open label trial returned after a 4 week interval and were retreated with up to 3 additional doses of infliximab. The timing of the additional doses was determined by disease relapse. Repeat administration again resulted in significant clinical improvement with minimal adverse effects. The improvement interval between doses, however, became progressively shorter during the course of the study. Additionally, 4 of the 8 patients developed HACA; antibody development may well account for the decreasing response duration observed during the course of the study.

In a double blind, placebo controlled trial, 101 patients were given intravenous infliximab (1, 3, or 10 mg/kg) with or without MTX (7.5 mg/week) or MTX plus intravenous placebo[209]. Sixty percent of patients receiving infliximab, with or without MTX, experienced at least 20% improvement in disease activity. Importantly, coadministration of low dose MTX significantly prolonged the duration of response seen with low dose (1 mg/kg) infliximab. Coadministration of MTX with higher doses of infliximab (3 and 10 mg/kg) also prolonged response duration, although not statistically significantly. All treatment arms were associated with minimal toxicity; headache was the most commonly observed adverse effect in patients receiving combination therapy. The overall incidence of HACA was 17% for patients receiving infliximab (with and without MTX), with the incidence inversely proportional to the dose of infliximab. Half the patients receiving low dose infliximab (1 mg/kg) without MTX developed HACA, compared with 7% of those receiving 10 mg/kg. Concurrent administration of low dose MTX greatly diminished development of HACA (by about 3-fold), suggesting that MTX induces an immunologic tolerance to infliximab.

Results from a 54 week, double blind, placebo controlled trial of infliximab in combination with MTX were reported[6]. Infliximab (3 mg/kg or 10 mg/kg intravenously) or placebo was given at 4 to 8 week intervals to patients with active RA who were also receiving MTX. Fifty-nine percent of patients receiving 10 mg/kg and 42% of those receiving 3 mg/kg at 4 to 8 week intervals experienced 20% improvement by ACR criteria. There were no statistically significant differences in percentage of responders among the infliximab groups. When compared to placebo, there was no increase in the incidence of adverse effects. The combination resulted in a statistically significant reduction in radiographic progression (measured by Sharp score) compared with MTX treatment alone.

PYRAMIDS, INVERTED PYRAMIDS, AND THERAPEUTIC PARADIGMS

Historical Evolution of the Current Approach

The therapeutic pyramid was the principle paradigm on which discussions of rheumatoid therapy were based for the last quarter century. It took time to develop as the different layers became available and/or accepted, but it took much less time to "self-destruct" once it was clear that its use was inappropriate and outmoded.

The beginnings of rheumatoid therapy in the 1930s were associated with better delineation of the disease, but apart from prescriptions of rest and casts, included a wide variety of what would now be regarded as "alternative" approaches, e.g., vaccine therapy, treatment of focal infections, bee stings, high dose vitamins, etc. Acetylsalicylic acid (ASA) was available and was used, often to tolerance; gold had been introduced, but was not widely used and did not reach North America until its introduction by Adams and Cecil in 1950 in the USA, and by Robinson in the spa town of Banff, Alberta, Canada.

The base of the pyramid. This was, in the 1940s and 1950s, the standard approach involving "physical medicine and rehabilitation." Splints were *de rigeur*, and were designed for a wide variety of uses including the prevention of ulnar deviation. Bed rest, correct posture in bed, and a bed exercise program were incorporated into most rheumatoid programs through the 1970s. As recently as 1971 Boyle and Buchanan's textbook[211] makes the point that "there is no agent which will significantly alter the course of this disease over a number of years." This may have been true, but part of the problem was that there remained in the 1950s and beyond a significant optimism about the outcome of RA in at least some academic circles. Thus, in 1955 both Duthie in Scotland and Ropes from Massachusetts agreed with "the findings that suggest a good prognosis..." in rheumatoid patients[212]. This is clearly a reflection of the quality and quantity of available outcome measures at that time. The wide variety of available physical therapies, including moist and dry heat, waxes, the proper use of cold, massage, and even heliotherapy and fever therapy, were generally accepted by most without any sense of a requirement to assess outcomes or effectiveness. However, as the period of clinical trials came into its infancy there was a controlled study in 1963 demonstrating the benefits of complete immobilization of a rheumatoid joint using splints for a 3 week period[213].

The next layers. ASA was traditionally included in "the base," but the evidence for a developing pyramidal approach was present in the 1960s. The Empire Rheumatism Council had had a successful trial of gold so

that its acceptance became wider, but Copeman's (UK) textbook in 1965 included the statement that "gold should never be the treatment of first choice in early cases, many of whom do remarkably well on simple conservative measures."[214] Thus, "second line" treatment began. Svartz had developed salazopyrine in 1939 with some seeming initial success. In this newly developing scientific approach a clinical study was designed to assess it, but the drug showed no benefit and was rejected[97]. This was because of faulty study design, including poor statistical methods, but also — a recurrent theme for many decades — poor outcome measures. However, the drug was not restudied and reintroduced as a "second line" agent until the mid-1970s.

NSAID. At this period, the first of the new (post-ASA) NSAID were introduced. They gradually gained acceptance as (short term) clinical studies showed they reduced pain and stiffness. These then became the second tier. As new ones arrived they were added, and some, like butazolidin, and to some degree indomethacin and fenamates, were virtually discarded, chiefly because of toxicity issues. The NSAID overall were considered very safe, again longer term outcome studies had not been carried out.

2nd line drugs. Antimalarials were recognized, but again fear of toxicity, in this case ocular, restricted their use. As dosages were standardized over the years this issue has now virtually disappeared. Penicillamine was added to this list and remains accepted, levamisole was also included in some countries, and while efficacious in short term studies, was rejected because of toxicity concerns, specifically agranulocytosis.

The apex. Azathioprine and cyclophosphamide — or other alkylating agents — occupied this position. They represented "last resort" options, and although azathioprine gained acceptance in the UK particularly, it was especially as a "steroid sparing" agent, i.e., allowing a reduction in the dose of systemic steroids used. This did not have a strong appeal.

In Copeman's 5th edition (1978), Carson Dick described 1st line, 2nd line, and 3rd line drugs with progression from one class to the next[215]. In 1985, prior to its immediate demise, the pyramid was published as a formal structure in McCarty's 10th edition[216].

Over the same period two other major areas of therapy were evolving — steroids and surgery.

Systemic corticosteroids. Systemic corticosteroids, initially cortisone and ACTH, but subsequently prednisone and prednisolone, were introduced after the dramatic demonstration of their efficacy in individual patients. It did not take long to recognize that there were definite risks attached to their use, and the "steroid honeymoon" did not last long. First, controlled trials of cortisone and later prednisone by the Empire Rheumatism Council were not able to show a disease modifying effect of cortisone, and while the data from the prednisone study could be interpreted as showing a decrease in radiologic progression, the side effects and death rate in this 2 year study can only be described as awesome[217]. Textbooks in the 1960s and 1970s devoted almost as much space to describing steroids and their side effects as they did to the rest of the therapeutic armamentarium combined. In 1964, Copeman, who had been a pioneer in the use of steroid therapy in the UK, said in his textbook, "it is clear that corticosteroids have a distinctly limited role in the treatment of rheumatoid arthritis."[214] Lightfoot, in the 1985 edition of McCarty's textbook, puts systemic steroids at the apex of the pyramid, above cytotoxic drugs[216]. Ward, however, pointed out even in 1990 that while "it is traditional teaching that systemic corticosteroids should not be used in the early treatment of rheumatoid arthritis, it is common practice to use them so."[218] This is borne out by tables in most therapeutic studies in RA from the US and elsewhere showing 50% of subjects receiving systemic steroids[1,2]. Pincus and others, including Corbett[3], have shown that those receiving steroids have an increased mortality. The data from Fries supported this, but were not consistent with the idea that it was merely a reflection of increased disease severity in those receiving steroids, in that he was not able to show an association for azathioprine and increased mortality[4]. Two recent controlled, prospective studies have shown a decrease in erosion progression in patients receiving low dose, 7.5 mg and 5 mg, of prednisone[219,220]. One of them curiously was not able to confirm symptomatic improvement, which was the usual reason for their use. This evidence is still not widely accepted, and remains controversial[221].

Some would argue that even if systemic corticosteroids do slow progression to some extent, the demonstrated negatives (not least an increase in mortality) markedly outweigh this advantage, and this is supported by cross sectional studies, but as yet there are no truly longterm trials available. If new therapies arrive that will allow the avoidance of systemic use of this potentially dangerous agent, many rheumatologists would be delighted. It is important to emphasize that the above discussion reflects chronic systemic use and not the use of local steroids.

Surgery. The other — much more positive — development that occurred alongside the sequential pyramidal approach to rheumatoid therapy is the surgical approach. Synovectomies, usually of the knees, were carried out in the 1930s, but the results then and subsequently were assessed only in the short term, and clearly recurrences were frequent. The procedure is much less frequent now as we recognize that the establishment of overall disease control is more important.

Arthrodesis was, and still remains, a "salvage" procedure. Many of these, e.g., knee and hip, provided major difficulties and had been largely abandoned. Some, e.g., fusion of joints in the wrist and mid-tarsals, can be very effective in relieving pain and thereby improving function, and are still in use.

Arthroplasty. The old procedure of excision arthroplasty is largely confined to the metatarsophalangeal joints, and occasionally the radial head, but it is the advent of joint replacement, and especially total joint replacement, that has relieved so much suffering. This began with the development of vitallium, initially used as a cup and then as a prosthesis (Austin-Moore). The introduction of cement by Charnley, associated with positive pressure laminar air flow and antibiotics to reduce infection, as well as better implant materials and engineering, has transformed these procedures. They remain an indication of the failure of medical treatment, but replacement of hips and knees is in regular, routine use; those for shoulders, ankles, and other small joints may also have a role to play but are less standard. Given the clear improvement in health related quality of life and function as a result, for example, of total hip replacement, it is tempting to hope that the increased mortality seen with poor function in RA may also be improved[222,223].

Methotrexate. Folic acid antagonists — initially aminopterin, and later the safer amethopterin — were first used at the time of steroid introduction, and perhaps for that reason were not pursued. Hoffmeister (1983) published a large series of patients treated with MTX whom he had followed for a mean of 15 years with safety and good outcomes[127]. Controlled trials followed and it was included into the pyramid. As the initial concerns regarding the potential for marrow failure and liver damage eased, its use became popular and in many cases it became the slow acting drug of choice, especially in North America, although in Europe sulfasalazine retained this role.

The fate of the pyramid. Despite its "fame" or notoriety, the pyramid was not in universal or even widespread use. The structure of the pyramid, and even the principle involved, were not widely agreed to or known by general physicians in North America. Thus, in many longitudinal series, e.g., Pincus[224] and Wolfe[225], patients were first seen in the specialized units after almost a decade, and often had not previously received DMARD therapy. This situation seems to persist, for in a recent publication on leflunomide the mean duration of disease at trial entry was 7 years, and 40% had had no previous DMARD therapy[135]. Furthermore, as Ward[218] pointed out, steroid use in most of these studies was between 50% and 70%, even in recently published studies — sometimes more often than the use of DMARD. Thus, even in its heyday, the pyramid was not being adhered to. Even the ACR guidelines suggest that DMARD are not always required, and that the introduction of steroids may precede or supplant their use.

Well prior to this, newer patient centered measurement techniques, e.g., HAQ, Arthritis Impact Measurement Scale[218], etc., had entered first into clinical trials and subsequently to patient care and longterm studies. Using such techniques, Pincus reviewed the poor outcomes of the then current treatment paradigms, and demonstrated the increased mortality associated with severe disease, and the validity of questionnaires, including self-care, as predictors of mortality; others have confirmed this in different clinical settings[1,224].

It was shortly after this that Wilske and Healy, reacting in part to Pincus's report of poor outcomes of conventional rheumatoid treatment, described a reevaluation of the therapeutic pyramid[226,227]. Their approach was more, rather than less, aggressive, initiating therapy with a combination of drugs with the aim of inducing remission and then gradually stepping down some of the therapeutic agents involved. This was based on an analogy with cancer chemotherapy, where a remission is the aimed for result, and frequently several drugs are used in combination to achieve this. McCarty in part agreed with their philosophy of intervening more aggressively and emphasized that, "there was no point in waiting to assess the effectiveness of NSAID ..." and agreed that the pyramid should be demolished[228].

Fries put forward an alternative approach, a saw-tooth strategy[229]. He reviewed the ARAMIS and subsequently other data that NSAID were probably as toxic as the so-called 2nd line drugs, if not more so, and he emphasized therefore the importance of early DMARD use, and continued DMARD use, with changes sequentially as various drugs failed. However, his innovation was that be recommended setting a ceiling of progression using the HAQ score, and that the treatment should be changed whenever progression occurred. NSAID were used as adjunctive therapy and not basal.

Combination chemotherapy has now become widely accepted, although the evidence base for much of it remains marginal in the extreme. Most physicians, however, seem to arrive at a combination by virtue of adding sequential DMARD to partial failures (or partial successes!). This was clearly not the concept provided by Wilske. Nevertheless, when this adding approach has been studied in appropriate trials, it has not been shown to be effective, with the exception of a MTX/cyclosporine study[230], and more impressively with the recent anti-TNF agents, and here, as with the etanercept/MTX combination, it is not clear that it is truly additive, i.e., that the same result could not have been achieved if the MTX had been discontinued[203]. On the other hand, the use of MTX with infliximab, while not demonstrably enhancing the efficacy of the antiserum, does seem to prolong its efficacy, perhaps by decreasing antichimeric antibody formation[209,231]. In addition, there are now two studies showing that the initiation of combination therapy is not associated with any increase in side effects, and appears to have induced a marked degree of improvement, sometimes with the much sought after remission[232,233]. The combination studied specifically has been MTX, sulfasalazine, and hydroxychloroquine. Rather like the period of the 1960s, many physicians remain concerned that

patients will have difficulty accepting this triple therapy approach, and perhaps some even remain unconvinced that RA can be a devastating disease.

McCarty described triple therapy with cyclophosphamide, azathioprine, and hydroxychloroquine in 1982. A followup in 1986[192] also showed patients who had achieved remission, and one of his measures of success was a decrease or discontinuation in the dose of prednisone. However, this combination was nevertheless not recommended by him because of the oncogenic effects of cyclophosphamide. Overall, while the combination and step down approach is not widely accepted, the patterns of DMARD utilization clearly show that initiation of DMARD therapy is now much earlier in the disease than before[234]. Many rheumatologists will introduce DMARD as soon as a firm diagnosis is established. Thus, early, as well as more aggressive combinations of therapy are current themes.

Biologics. The development of biologic therapies was widely heralded as a breakthrough in rheumatoid disease therapy. The initial short term, uncontrolled pilot studies, for example of anti-CD4 antisera, were so successful that it was even suggested that it would be unethical to carry out placebo controlled studies. Fortunately, science prevailed, for those therapies were in fact not found to be useful, and the principle of controlled studies has been retained as part of the initial assessment of the biologics, as for more traditional agents. It has also become clear that the role of controlled clinical studies, while crucial, is limited, partly because of multiple exclusions to study entry, but also because longterm clinical followup studies, including measures of function, structure, and if possible behavior, are needed to assess effectiveness.

In 1991 a number of groups came together in a WHO/ILAR sponsored meeting, and a minimal core set for DMARD studies was adopted, including a measure of function. At this time new terminology was agreed upon. The terminology was changed: thus the term 2nd line agents became inappropriate as the introduction was advised early in the course of the disease. Slow acting was less valid as MTX, for example, began to work in some weeks. Disease modifying — DMARD — remains in vogue, although whether MTX always modifies the disease process any more than NSAID do is still unclear. Edmonds, *et al*[235] suggested the term DC-ART (disease controlling antirheumatic therapy) for those drugs of whatever type that had been shown to control radiologic progression of disease in studies of one year or longer. Thus, at least one of the currently approved biologic agents would be the first of the new biologics to fit under the heading of a one year DC-ART, although the demonstrated efficacy was in combination with low dose MTX, which might therefore complicate this designation. This approach recognizes the key role of joint protection — as assessed primarily radiologically — in the longterm management of RA.

Current and Future Issues

There is general agreement that rheumatoid inflammation should be controlled as completely as possible, as soon as possible, and that this control should be maintained for as long as possible, consistent with patient safety. The risk of RA management has decreased as rheumatologists have gained more experience using combinations of DMARD, and as increasingly specific and less toxic agents (e.g., TNF inhibitors, COX-2 inhibitors) have become available to modify inflammation. Potential benefit has increased with the documentation of DC-ART properties for a number of interventions, and prevention of structural damage will be emphasized in the development of new treatments. This improved therapeutic risk/benefit and the progressive, irreversible nature of RA joint damage justify immediate initiation of DMARD treatment of newly diagnosed RA, and this is rapidly becoming the expected standard of care.

Unfortunately, most patients achieve only partial suppression of rheumatoid inflammation and many lose therapeutic benefit after an initial good response. Additive combination therapy is the usual response to this, but also may produce only temporary benefit. The management of persistent or recurrent rheumatoid inflammation and disability continues to be a challenge, and it is not clear whether the future addition of more potent specific interventions in the immunoinflammatory process will be able to solve this problem without disarming host defenses against infections and tumors.

Another problem is the temporary benefit of current treatments. Even in patients with a complete response, RA manifestations almost always recur after the treatment is stopped, confirming the non-curative nature of the treatments. The etiology of RA remains as obscure as ever, and a search for curative treatments is not likely to be fruitful without more knowledge about a cause.

REFERENCES

1. Pincus T, Callahan LF, Vaughn WK, et al. Questionnaire, walking time, and button test measures of functional capacity as predictive markers for mortality in rheumatoid arthritis. J Rheumatol 1987;14:240-51.
2. Callahan LF, Pincus T, Huston JW, et al. Measures of activity and damage in rheumatoid arthritis depiction of changes and prediction of mortality over 5 years. Arthritis Care Res 1997;10:381-94.
3. Corbett M, Dalton S, Young A, Silman A, Shipley M. Factors predicting death, survival and functional outcome in a prospective study of early rheumatoid disease over 15 years. Br J Rheumatol 1993;32:717-23.
4. Leigh JP, Fries JF. Mortality predictors among 263 patients with rheumatoid arthritis. J Rheumatol 1991;18:1307-12.
5. Sharp JT, Strand V, Leung H, Hurley F, Loew-Friedrich I. Treatment with leflunomide slows radiographic progression of RA. Results from three randomized controlled trials of leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum 2000;43:495-505.
6. Lipsky PE, van der Heidje DM, St. Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594-602.
7. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586-93.
8. Guidance for Industry. Clinical development programs for drugs, devices and biological products for the treatment of rheumatoid arthritis. US, DHHS, FDA, Feb. 1999:www.fda.gov
9. Rodnan GP, Benedek TG. The early history of antirheumatic drugs. Arthritis Rheum 1970;13:145-65.
10. Gross M, Greenberg L. The salicylates. New Haven: Hillhouse Press; 1948.
11. Illingworth RS, Burke J, Doxiades SA, et al. Salicylates in rheumatic fever: an attempt to assess their value. Q J Med 1954;23:177-213.
12. Ansell BM, Bywater EGL. Prognosis in Still's disease. Bull Rheum Dis 1959;9:189-92.
13. Clements PJ, Paulus HE. Nonsteroidal antirheumatic drugs. In: Kelly W, et al, editors. Textbook of rheumatology. 5th ed. Philadelphia: Sanders;1997:707-40.
14. Vane JR. Inhibition of prostaglandin synthesis as the mechanism of action for aspirin-like drugs. Nature New Biol 1971;231:232-5.
15. Masferrer JL, Zweifel BS, Seibert K, Needleman P. Selective regulation of cellular cyclooxygenase by dexamethasone and endotoxin in mice. J Clin Invest 1990;86:1375-9.
16. Gierse JK, Hauser SD, Creely DP, et al. Expression and selective inhibition of the constitutive and inducible forms of human cyclooxygenase. II. J Biochem 1995;305:479-84.
17. Crofford LJ, Lipsky PE, Brooks P, Abramson SB, Simon LS, van de Putte LBA. Basic biology and clinical applications of specific cyclooxygenase-2 inhibitors. Arthritis Rheum 2000;43:4-13.
18. Lipsky PE, Brooks P, Crofford LJ, et al. Unresolved issues in the role of cyclooxygenase-2 in normal physiologic processes and disease. Arch Intern Med 2000;160:913-20.
19. Furst DE. Pharmacology and efficacy of cyclooxygenase (COX) inhibitors. Am J Med 1999;107:18-S-26-S.
20. Fries JF. NSAID gastropathy: the second most deadly rheumatic disease? Epidemiology and risk appraisal. J Rheumatol 1991;18 Suppl 28:6-10.
21. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. Ann Intern Med 1995;123:241-9.
22. Forestier J. Rheumatoid arthritis and its treatment by gold salts. J Lab Clin Med 1935;20:837-40.
23. Fraser TN. Gold therapy in rheumatoid arthritis. Ann Rheum Dis 1945;4:71-5.
24. Empire Rheumatism Council. Gold therapy in rheumatoid arthritis. Report of a multicenter controlled trial. Ann Rheum Dis 1961;20:315-34.
25. Gottlieb NL, Kiem IM, Penneys NS, et al. The influence of chrysotherapy on serum proteins and immunoglobulin levels, rheumatoid factor, and antiepithelial antibody titers. J Lab Clin Med 1975;86:962-72.
26. Highton J, Panayi GS, Shephard P, Faith A, Griffin J, Gibson T. Fall in immune complex levels during gold treatment of rheumatoid arthritis. Ann Rheum Dis 1981;40:575-9.
27. Sigler JW, Bluhm GB, Duncan H, et al. Gold salts in the treatment of rheumatoid arthritis: a double-blind study. Ann Intern Med 1974;80:21-6.
28. Sharp JT, Lidsky MD, Duffy J. Clinical responses during gold therapy for rheumatoid arthritis: changes in synovitis, radiologically detectable erosive lesions, serum proteins, and serologic abnormalities. Arthritis Rheum 1982;25:540-9.
29. Adams CH, Cecil RL. Gold therapy in early rheumatoid arthritis. Ann Intern Med 1950;33:163-73.
30. Rothermich NO, Phillips VK, Bergen W. Chrysotherapy: a prospective study. Arthritis Rheum 1976;19:1321-7.
31. Srinivasan R, Miller BL, Paulus HE. Long-term chrysotherapy in rheumatoid arthritis. Arthritis Rheum 1979;22:105-10.
32. Sambrook TN, Browne CD, Champion GD, Day RO, Vallance JB, Warwick N. Termination of treatment with gold sodium thiomalate in rheumatoid arthritis. J Rheumatol 1982;9:932-4.
33. Richter JA, Runge LA, Pinals RS, Oates RP. Analysis of treatment terminations with gold and anti-malarial compounds in rheumatoid arthritis. J Rheumatol 1980;7:153-9.
34. Epstein WV, Henke CJ, Yelin EH, Katz PP. Effect of parenterally administered gold therapy on the course of adult rheumatoid arthritis. Ann Intern Med 1991;114:437-44.
35. Wallace D. Antimalarial agents and lupus. Rheum Dis Clin North Am 1994;20:243-63.
36. Cohen A, Calkins E. A controlled study of chloroquine as an antirheumatic agent. Arthritis Rheum 1958;1:297-308.
37. Freedman A, Steinberg VL. Chloroquine in rheumatoid arthritis: a double blindfold trial of treatment for one year. Ann Rheum Dis 1960;19:243-50.
38. Popert A, Meijers K, Sharp J. Chloroquine in rheumatoid arthritis. Ann Rheum Dis 1961;20:18-28.
39. Scull E. Chloroquine and hydroxychloroquine therapy in rheumatoid arthritis. Arthritis Rheum 1962;5:30.
40. Hamilton E, Scott J. Hydroxychloroquine in treatment of rheumatoid arthritis. Arthritis Rheum 1962;5:502-12.
41. Mainland D, Sutcliffe MI. Hydroxychloroquine in rheumatoid arthritis: a six-month, double-blind trial. Bull Rheum Dis 1962;13:287-90.
42. HERA. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: The HERA study. Am J Med 1995;98:156-68.
43. Laaksonen L, Koskiadhde V, Juva K. Dosage of antimalarial drugs for children with juvenile RA. Scand J Rheumatol 1974;3:103-8.
44. Clark P, Casas E, Tugwell P, et al. Hydroxychloroquine compared with placebo in rheumatoid arthritis. Ann Intern Med 1993;119:1067-71.
45. Furst DE, Lindsley H, Baethge B, et al. Dose-loading with hydroxychloroquine improves the rate of response in early, active rheumatoid arthritis. Arthritis Rheum 1999;42:357-65.
46. Shearer R, Dubois E. Ocular changes induced by long-term hydroxychloroquine therapy. Am J Ophthalmol 1967;65:245-51.
47. Reed H, Karlinskyh W. Delayed onset of chloroquine retinopathy. Can Med Assoc J 1967;97:1408-11.
48. Bernstein HN. Ocular safety of hydroxychloroquine. Ann Ophthalmol 1991;23:292-6.
49. Nylander U. Ocular damage in chloroquine retinopathy. Acta Ophthalmol (Copenh) 1966;44:335-40.
50. Cox NH, Paterson WD. Ocular toxicity of antimalarials in dermatology: a survey of current practice. Br J Dermatol 1994;131:878-82.
51. Brinkley J, Dubois E, Ryan S. Long-term course of chloroquine retinopathy after cessation of medication. Am J Ophthalmol 1979;88:1-11.
52. Rynes R. Ophthalmologic safety of long-term hydroxychloroquine treatment. Am J Med 1983;78:204-10.
53. Finbloom DS, Silver K, Newsome DA, et al. Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. J Rheumatol 1985;12:692-4.
54. Whisnant J, Espinosa R, Kierland R, et al. Chloroquine neuromyopathy. Mayo Clin Proc 1963;23:502-10.
55. Ratliff N. Diagnosis of chloroquine cardiomyopathy by endomyocardial biopsy. N Eng J Med 1987;316:191-204.
56. Begg T, Simpson J. Chloroquine neuromyopathy. BMJ 1964; 1:770-2.
57. Loftus L. Peripheral neuropathy following chloroquine therapy. Can Med Assoc J 1963;89:917-20.
58. McDuffie F. Bone marrow depression after drug therapy of SLE and

rheumatic diseases. Ann Rheum Dis 1965;24:289-94.
59. Polano M, Cats A, Van Older G. Agranulocytosis following treatment with hydroxychloroquine. Lancet 1965;1:1275-6.
60. Propp R, Stillman J. Agranulocytosis and hydroxychloroquine. N Eng J Med 1967;244;492-3.
61. Unanue E. Antigen-presenting function of the macrophages. Annu Rev Immunol 1984;2:395-428.
62. Cohen S, Yielding K. Inhibition of DNA and RNA polymerase reactions by chloroquine. Proc Natl Acad Sci USA 1991;88:3150-4.
63. Filippov A, Skatova G, Porotikov V, et al. Ca++ antagonistic properties of phospholipase A_2 inhibitors, mepacrine and chloroquine. Gen Physiol Biophys 1989;8:113-8.
64. Hurst NP, French JK, Gorjatschko L, et al. Chloroquine and hydroxychloroquine inhibit multiple sites in metabolic pathways leading to neutrophil superoxide release. J Rheumatol 1988;15:23-7.
65. Salmeron G, Lipsky PE, Immunosuppression potentials of antimalarials. Am J Med 1983;75 Suppl 1a:19-24.
66. Picot S, Peyron F, Donadille A, et al. Chloroquine-induced inhibition of the production of TNF, but not IL-6, is affected by disruption of iron metabolism. Immunology 1993;80:127-33.
67. Naimiuchi S, Kumagai S, Imura H, et al. Quinacrine inhibits the primary but not secondary proliferative response of human cytotoxic T cells to allogeneic non T-cell antigens. J Immunol 1984; 123:1456-61.
68. Abraham EP, Chain E, Baker W, Robinson R. Penicillamine: a characteristic degradation product of penicillin. Nature 1943;151:107.
69. Jaffe IA. Comparison of the effect of plasmapheresis and penicillamine on the level of circulating rheumatoid factor. Ann Rheum Dis 1963;1:588-90.
70. Huskisson EC, Gibson TJ, Balme HW, et al. Trial comparing D-penicillamine in rheumatoid arthritis: preliminary report. Ann Rheum Dis 1974;33:532-5.
71. Berry H, Liyange R, Durance CG, Berger L. Trial comparing azathioprine and penicillamine in treatment of rheumatoid arthritis. Ann Rheum Dis 1976;35:542-3.
72. Dixon A St J, Davis J, Dormandy TL, et al. Synthetic (D(-) penicillamine in rheumatoid arthritis. Arthritis Rheum 1965; 34:416-21.
73. Jaffe IA. The technique of penicillamine administration in rheumatoid arthritis. Arthritis Rheum 1975;18:513-4.
74. Jaffe IA. D-penicillamine. Bull Rheum Dis 1978;28:948-52.
75. Levy J, Paulus HE, Barnett EV, et al. A double-blind controlled evaluation of azathioprine treatment in rheumatoid arthritis and psoriatic arthritis. Arthritis Rheum 1972;15:116-7.
76. Urowitz MB, Gordon DA, Smythe HA, et al. Azathioprine in rheumatoid arthritis. A double-blind, cross-over study. Arthritis Rheum 1973;16:411-8.
77. Urowitz MB, Hunter T, Bookman AAM, et al. Azathioprine in rheumatoid arthritis: a double-blind study comparing full dose to half dose. J. Rheumatol 1974;1:274-81.
78. Hunter T, Urowitz MB, Gordon DA, et al. Azathioprine in rheumatoid arthritis. A long-term follow-up study. Arthritis Rheum 1975;18:15-20.
79. Pinals RS. Azathioprine in the treatment of chronic polyarthritis: long-term results and adverse effects in 25 patients. J Rheumatol 1976;3:140-4.
80. DeSilva M, Hazleman BL. Long-term azathioprine in rheumatoid arthritis: a double-blind study. Ann Rheum Dis 1981;40:560-3.
81. Thompson PW, Kirwan JR, Barnes CG. Practical results of treatment with disease-modifying antirheumatoid drugs. Br J Rheumatol 1985;24:167-75.
82. Turk JL, Parker D, Poulter LW. Functional aspects of the selective depletion of lymphoid tissue by cyclophosphamide. Immunology 1972;23:493-501.
83. Lagrange PH, MacKaness GB, Miller TE. Potentiation of T-cell-mediated immunity by selective suppression of antibody formation with cyclophosphamide. J Exp Med 1974;139:1529-39.
84. Kerkhaert JAM, Hofhuis FMA, Willers JMN. Influence of cyclophosphamide on delayed hypersensitivity and acquired cellular resistance to Listeria monocytogenes in the mouse. Immunology 1977;32:1027-32.
85. Rollinghoff M, Starzinski-Powitz A, Pfizenmaier K, et al. Cyclophosphamide-sensitive T-lymphocytes suppress the in vivo generation of antigen-specific cytotoxic T-lymphocytes. J Exp Med 1977;45:455-9.
86. Ferguson RM, Simmons RL. Differential cyclophosphamide sensitivity of suppressor and cytotoxic cell precursors. Transplantation 1978;25:36-8.
87. Currey HLF, Harris J, Mason RM, et al. Comparison of azathioprine, cyclophosphamide and gold in treatment of rheumatoid arthritis. BMJ 1974;3:763-6.
88. Berry H, Liyanage SP, Durance RA, et al. Trial comparing azathioprine and penicillamine in treatment of rheumatoid arthritis. Ann Rheum Dis 1976;35:542-43.
89. Singh G, Fries JF, Spitz R, et al. Toxic effects of azathioprine in rheumatoid arthritis: a national postmarketing perspective. Arthritis Rheum 1989;32:837-43.
90. Paulus HE, Williams HJ, Ward JR, et al. Azathioprine vs. D-penicillamine in rheumatoid arthritis patients who have been treated unsuccessfully with gold. Arthritis Rheum 1984;27:721-7.
91. Diaz CJ, Garcia EL, Mechante T. Treatment of rheumatoid arthritis with nitrogen mustard. Preliminary report. JAMA 1951;147:1418-9.
92. Fosdick WM, Parsons JL, Hill DF. Long-term cyclophosphamide therapy in rheumatoid arthritis. Arthritis Rheum 1968;11:151-60.
93. Smyth CJ, Bartholomew BA, Mills DM, et al. Cyclophosphamide therapy for rheumatoid arthritis. Arch Intern Med 1975;135:789-93.
94. Williams HJ, Klauber MR, O'Brien WM, et al. Comparison of high and low dose cyclophosphamide therapy in rheumatoid arthritis. Arthritis Rheum 1980;23:521-7.
95. Townes AS, Sowa JM, Shulman LE. Controlled trials of cyclophosphamide in rheumatoid arthritis. Arthritis Rheum 1976;19:563-73.
96. Cooperating Clinical Committee of the American Rheumatism Association. A controlled trial of cyclophosphamide in rheumatoid arthritis. N Engl J Med 1970;283:883-9.
97. Sinclair RJG, Duthie JJR. Salasopyrin in the treatment of rheumatoid arthritis. Ann Rheum Dis 1949;8:226-31.
98. McConkey B, Amos RS, Butler EP, et al. Salazopyrin in rheumatoid arthritis. Agents Actions 1978;8:438-41.
99. McConkey B, Amos RS, Durham S, et al. Sulphasalazine in rheumatoid arthritis. BMJ 1980;280:442-4.
100. Neumann VC, Grindulis KA, Hubbal S, et al. Comparison between penicillamine and sulphasalazine in rheumatoid arthritis: Leeds-Birmingham trial. BMJ 1983;287:1099-102.
101. Williams HJ, Ward JR, Dahl SL, et al. A controlled trial comparing sulfasalazine, gold sodium thiomalate, and placebo in rheumatoid arthritis. Arthritis Rheum 1988;31:702-13.
102. Pinals RS, Kaplan SB, Lawson JG, Hepburn B. Sulfasalazine in rheumatoid arthritis: a double-blind, placebo-controlled trial. Arthritis Rheum 1986;29:1447-34.
103. Bax DE, Amos RS. Sulphasalazine: a safe, effective agent for prolonged control of rheumatoid arthritis. A comparison with sodium aurothiomalate. Ann Rheum Dis 1985;44:194-8.
104. Gubner R, August S, Ginsberg V. Therapeutic suppression of tissue reactivity. II. Effect of aminopterin in rheumatoid arthritis and psoriasis. Am J Med Sci 1951;221:176-82.
105. Black RL, O'Brien WM, Van Scott EJ, Auerbach R, Eisen Z, Bunim JJ. Methotrexate therapy in psoriatic arthritis. Double-blind study on 21 patients. JAMA 1964;189:743-7.

106. Weinblatt ME, Coblyn JS, Fox DA, et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. N Eng J Med 1985; 312:818-22.
107. Andersen PA, West SG, O'Dell JR, Via CS, Claypool RG, Kotzin BL. Weekly pulse methotrexate in rheumatoid arthritis. Clinical and immunologic effects in a randomized, double-blind study. Ann Intern Med 1985;103:489-96.
108. Thompson RN, Watts C, Edelman J, Esdaile J, Russell AS. A controlled two-centre trial of parenteral methotrexate therapy for refractory rheumatoid arthritis. J Rheumatol 1984;11:760-3.
109. Williams HJ, Willkens RF, Samuelson COG, et al. Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis. A controlled clinical trial. Arthritis Rheum 1985;28:721-30.
110. Tugwell P, Bennett K, Gent M. Methotrexate in rheumatoid arthritis. Indications, contraindications, efficacy, and safety. Ann Intern Med 1987;107:358-66.
111. Sega R, Mozes E, Yaron M, Tartakovsky B. The effects of methotrexate on the production and activity of interleukin-1. Arthritis Rheum 1989;32:370-7.
112. Barrera P, Boerbooms AM, Demacker PN, van de Putte LB, Gallati H, van der Meer JW. Circulating concentrations and production of cytokines and soluble receptors in rheumatoid arthritis patients: effects of a single dose methotrexate. Br J Rheumatol 1994;33:1017-24.
113. Crilly A, McInness AG, Watson J, Capell HA, Madhok R. Interleukin-6 and soluble IL-2 receptor levels in patients with rheumatoid arthritis treated with low dose oral methotrexate. J Rheumatol 1995;22:224-6.
114. Sperling RI, Coblyn JS, Larkin JK, Benincaso AI, Austen KF, Weinblatt ME. Inhibition of leukotriene B4 synthesis in neutrophils from patients with rheumatoid arthritis by a single oral dose of methotrexate. Arthritis Rheum 1990;33:1149-55.
115. Sperling RI, Benincaso AI, Anderson RJ, Coblyn JS, Austen KF, Weinblatt ME. Acute and chronic suppression of leukotriene B4 synthesis ex vivo in neutrophils from patients with rheumatoid arthritis beginning treatment with methotrexate. Arthritis Rheum 1994;12:643-8.
116. Michaels RM, Chang ZL, Beezhold DH. Phospholipase A2 activity in peripheral blood cells of rheumatoid arthritis patients treated with methotrexate: a preliminary study. Clin Exp Rheumatol 1994;12:643-8.
117. Olsen NJ, Callahan LR, Pincus T. Immunologic studies of rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum 1987;30:481-8.
118. Alarcon GS, Schrohenloher RE, Bartolucci AA, Ward JR, Williams HJ. Suppression of rheumatoid factor production by methotrexate in patients with rheumatoid arthritis. Evidence for differential influences of therapy and clinical status on IgM and IgA rheumatoid factor expressions. Arthritis Rheum 1990;33:1156-61.
119. Van der Veen MJ, van der Heide A, Kruize AA, Bijlsma JW. Infection rate and use of antibiotics in patients with rheumatoid arthritis treated with methotrexate. Ann Rheum Dis 1994;53:224-8.
120. Szanto E. Low-dose methotrexate treatment of rheumatoid arthritis; long-term observation of efficacy and safety. Clin Rheumatol 1989;8:323-30.
121. Kremer JM, Lee JK. The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. Arthritis Rheum 1986;29:822-31.
122. Kremer JR, Lee JK. A long-term prospective study of the use of methotrexate in rheumatoid arthritis. Update after a mean of fifty-three months. Arthritis Rheum 1992;31:577-84.
123. Weinblatt ME, Trentham DE, Fraser PA, et al. Long-term prospective trial of low-dose methotrexate in rheumatoid arthritis. Arthritis Rheum 1988;31:167-75.
124. Kremer JM, Phelps CT. Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis. Update after a mean of 90 months. Arthritis Rheum 1992;35:138-45.
125. Weinblatt ME, Maier AL. Longterm experience with low dose weekly methotrexate in rheumatoid arthritis. J Rheumatol 1990;17:33-8.
126. Buchbinder R, Hall S, Sambrook PN, et al. Methotrexate therapy in rheumatoid arthritis: a life table review of 587 patients treated in community practice. J Rheumatol 1993;20:639-44.
127. Hoffmeister RT. Methotrexate therapy in rheumatoid arthritis: 15 years experience. Am J Med 1983;75:69-73.
128. Weinblatt ME, Weissman BN, Holdsworth DE, et al. Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis. 84-month update. Arthritis Rheum 1992;35:129-37.
129. Alarcon GS, Tracy IC, Blackburn WD Jr. Methotrexate in rheumatoid arthritis. Toxic effects as the major factor in limiting long-term treatment. Arthritis Rheum 1989;32:671-6.
130. Furst DE, Erikson N, Clute L, Koehnke R, Burmeister LF, Kohler JA. Adverse experience with methotrexate during 176 weeks of a longterm prospective trial in patients with rheumatoid arthritis. J Rheumatol 1990;17:1628-35.
131. Felson DT, Anderson JJ, Meenan RJ. Use of short-term efficacy/toxicity tradeoffs to select second-line drugs in rheumatoid arthritis. A metaanalysis of published clinical trials. Arthritis Rheum 1992;35:1117-25.
132. Lopez-Mendez A, Daniel WW, Reading JC, Ward JR, Alarcon GS. Radiographic assessment of disease progression in rheumatoid arthritis patients enrolled in the Cooperative Systemic Studies of the Rheumatic Diseases Program randomized clinical trial of methotrexate, auranofin, or a combination of the two. Arthritis Rheum 1993;35:1365-9.
133. Nordstrom DM, West SG, Andersen PA, Sharp JT. Pulse methotrexate therapy in rheumatoid arthritis. A controlled prospective roentgenographic study. Ann Intern Med 1987; 107:797-801.
134. Reykdal S, Steinsson K, Sigurjonsson K, Brekkan A. Methotrexate treatment of rheumatoid arthritis: effects on radiographic progression. Scand J Rheumatol 1989;18:221-6.
135. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with leflunomide compared to placebo and methotrexate. Arch Intern Med 1999;159:2542-50.
136. Bannwarth B, Labat L, Moride Y, Schaeverbeke T. Methotrexate in rheumatoid arthritis. An update. Drugs 1994;47:25-50.
137. Brick JE, Moreland LW, Al-Kawas F, Chang WWL, Layne RD, DeBartolomeo AG. Prospective analysis of liver biopsies before and after methotrexate therapy in rheumatoid arthritis. Semin Arthritis Rheum 1989;18:1-14.
138. Ahern MJ, Kevat S, Hill W, Hayball PJ, Harley H, Hall PM. Hepatic methotrexate content and progression of hepatic fibrosis: preliminary findings. Ann Intern Med 1991;50:477-80.
139. Kremer JM, Lee RG, Tolman KG. Liver histology in rheumatoid arthritis patients receiving long-term methotrexate therapy. A prospective study with baseline and sequential biopsy samples. Arthritis Rheum 1989;32:121-7.
140. Aponte J, Petrelli M. Histopathologic findings in the liver of rheumatoid arthritis patients treated with long-term bolus methotrexate. Arthritis Rheum 1988;31:1457-64.
141. Shergy WJ, Polisson RP, Caldwell DS, Rice JR, Pisetsky DS, Allen NB. Methotrexate-associated hepatotoxicity: retrospective analysis of 210 patients with rheumatoid arthritis. Am J Med 1988;85:771-4.
142. Whiting-O'Keefe QE, Fye KH, Sack KD. Liver biopsy and methotrexate use: see no evil? Methotrexate and histologic abnormalities: a meta-analysis. Am J Med 1991;70:711-6.
143. Kremer JM, Galivan J, Streckfuss A, Kamen B. Methotrexate metabolism analysis in blood and liver of rheumatoid arthritis

patients. Association with hepatic folate deficiency and formation of polyglutamates. Arthritis Rheum 1986;29:832-5.

144. Bjorkman DJ, Hammond EH, Lee RG, Clegg DO, Keith GT. Hepatic ultrastructure after methotrexate therapy for rheumatoid arthritis. Arthritis Rheum 1988;31:1465-72.

145. Kremer JM, Alarcon GS, Lightfoot RW Jr, et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. Arthritis Rheum 1994;37:316-28.

146. Carroll GJ, Thomas R, Phatouros CC, et al. Incidence, prevalence and possible risk factors for pneumonitis in patients with rheumatoid arthritis receiving methotrexate. J Rheumatol 1994;21:51-4.

147. White DA, Rankin JA, Stover DE, Gellene RA, Gupta S. Methotrexate pneumonitis. Bronchoalveolar lavage findings suggest an immunologic disorder. Am Rev Respir Dis 1989;139:18-21.

148. St. Clair EW, Rice JR, Snyderman R. Pneumonitis complicating low-dose methotrexate therapy in rheumatoid arthritis. Arthritis Rheum 1983;26:1269-78.

149. Ridley WG, Wolfe CS, Mathews JA. Life threatening acute pneumonitis during low dose methotrexate treatment for rheumatoid arthritis: a case report and review of the literature. Ann Rheum Dis 1988;47:784-8.

150. Cannon GW, Ward JR, Clegg DO, Samuelson CO Jr, Abbott TM. Acute lung disease associated with low-dose pulse methotrexate therapy in patients with rheumatoid arthritis. Arthritis Rheum 1983;26:1269-74.

151. Alarcon GS, Gispen JG, Koopman WJ. Severe reversible interstitial pneumonitis induced by low dose methotrexate. J Rheumatol 1989;16:1007-8.

152. Engelbrecht JA, Calhoon SL, Scherrer JJ. Methotrexate pneumonitis after low-dose therapy for rheumatoid arthritis. Arthritis Rheum 1983;26:1275-8.

153. Clarysse AM, Cathey WJ, Cartwright GE, Wintrobe MM. Pulmonary disease complicating intermittent therapy with methotrexate. JAMA 1969;209:1861-4.

154. Krause D, Schleusser B, Herborn G, Rau R. Response to methotrexate treatment is associated with reduced mortality in patients with severe rheumatoid arthritis. Arthritis Rheum 2000;43:14-21.

155. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomized, multicenter trial. European Leflunomide Study Group. Lancet 1999;353:259-66.

156. Emery P. Disease modification in rheumatoid arthritis with leflunomide. Scand J Rheumatol 1999;Suppl 112:9-14.

157. Weinblatt ME, Kremer JM, Coblyn JS, et al. Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum 1999;42:1322-8.

158. Sigal NH, Dumont FG. Cyclosporin A, FK-506, and rapamycin. Pharmacologic probes of lymphocyte signal transduction. Ann Rev Immunol 1992;10:519-60.

159. Braun W, Kallen J, Mikol V, Walkinshaw MD, Wuthrich K. Three-dimensional structure and actions of immunosuppressants and their immunophilins. FASEB J 1995;9:63-72.

160. Kronke M, Leonard WJ, Depper MJ, et al. Cyclosporin A inhibits T cell growth factor gene expression at the level of mRNA transcription. Proc Natl Acad Sci USA 1984;81:5214-8.

161. Kay Je, Kromwel L, Doe SEA, Denyer M. Inhibition of T and B lymphocyte proliferation by rapamycin. Immunol 1991;72:544-9.

162. Herrmann B, Mueller W. Die Therapie der chronischen polyarthritis mit Cyclosporin A, einen neuen immune-suppressivum. Akt Rheumatol 1979;4:173-86.

163. Amor B, Dougados M. Cyclosporin in rheumatoid arthritis. Open trials with different dosages. In: Schindler R, ed. Cyclosporin in autoimmune diseases. Berlin: Springer; 1985:283-7.

164. Dougados M, Amor B. Cyclosporin A in rheumatoid arthritis. Preliminary clinical results of an open trial. Arthritis Rheum 1987;30:83-7.

165. Bowles CA. Long-term treatment of rheumatoid arthritis with cyclosporin [abstract]. Arthritis Rheum 1989;32 Suppl:S61.

166. Weinblatt ME, Coblyn JS, Fraser PA, et al. Cyclosporine A treatment of refractory rheumatoid arthritis. Arthritis Rheum 1987;30:11-7.

167. Tugwell P, Bombardier C, Gent M, et al. Low dose cyclosporin in rheumatoid arthritis. A pilot study. J Rheumatol 1987;14:1108-14.

168. Dougados M, Duchesne L, Awada J, Amor B. Assessment of efficacy and acceptability of low dose cyclosporin in patients with rheumatoid arthritis. Ann Rheum Dis 1989;48:550-6.

169. Forre O, Bjerkhoel F, Salvesen CF, et al. An open, controlled, randomized comparison of cyclosporine and azathioprine in the treatment of rheumatoid arthritis. A preliminary report. Arthritis Rheum 1987;30:88-92.

170. Van Rijthoven AWAM, Dijkmans BAC, Goei The HS, et al. Comparison of cyclosporine and D-penicillamine for rheumatoid arthritis. A randomized, double-blind multicenter study. J Rheumatol 1991;18:815-20.

171. Schattenkirchner M, Kruger K. Cyclosporine vs azathioprine in the treatment of rheumatoid arthritis, a controlled double blind study [abstract]. 2nd Congress on Immunointervention in Autoimmune Diseases, Paris, 1991:198.

172. Forre O, Norwegian Arthritis Disease Study Group. Cyclosporine as a disease modifier in rheumatoid arthritis [abstract]. 2nd Congress on Immunointervention in Autoimmune Diseases, Paris, 1991:197.

173. Tugwell P, Bombardier C, Gent M, et al. Low dose cyclosporin versus placebo in patients with rheumatoid arthritis. Lancet 1990;335:1051-5.

174. Yocum DE, Klippel JH, Wilder RL, et al. Cyclosporin A in severe, treatment-refractory rheumatoid arthritis. A randomized study. Ann Intern Med 1988;109:863-9.

175. Dougados M, Awada H, Amor B. Cyclosporin in rheumatoid arthritis. A double blind, placebo controlled study in 52 patients. Ann Rheum Dis 1988;47:127-33.

176. Van Rijthoven AWAM, Dijkmans BAC, Goei The HS, et al. Cyclosporin treatment for rheumatoid arthritis. A placebo controlled, double-blind, multicenter study. Ann Rheum Dis 1986;45:726-31.

177. McCarty DJ, Harman JG, Grassanovich JL, Qian C, Klein JP. Combination drug therapy of seropositive rheumatoid arthritis. J Rheumatol 1995;22:1636-45.

178. Bensen W, Tugwell P, Roberts RM. Combination therapy of cyclosporine with methotrexate and gold in rheumatoid arthritis (2 pilot studies). J Rheumatol 1994;21:2034-8.

179. Verhoeven AC, Boers M, Tugwell P. Combination therapy in rheumatoid arthritis: Updated systematic review. Br J Rheumatol 1998;37:612-9.

180. O'Dell J. Combination DMARD therapy for rheumatoid arthritis: Apparent universal acceptance [abstract]. Arthritis Rheum 1997;40 Suppl:S50.

181. Wolfe F, Pincus T, Fries JR, and the UA Inception Cohort Group: Use of second line "disease-modifying" anti-rheumatic drugs within 5 months of disease onset by 64% of 750 rheumatoid arthritis patients under care of 142 US rheumatologists: An inception cohort study [abstract]. Arthritis Rheum 1997;40 Suppl:S218.

182. Wolfe F, Hawley DJ. Remission in rheumatoid arthritis. J Rheumatol 1985;12:245-52.

183. Luukkainen R, Kajander A, Isomaki H. Effect of gold on progression of erosions in rheumatoid arthritis: Better results with early treatment. Scand J Rheumatol 1997;6:189-92.

184. Van der Heijde DMFM, van Riel PLCM, Nuver-Zwart IH, Gribnau FJW, van de Putte LBA. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036-8.

185. Rau R, Schattenkirchner M, Muller-Passbender H, Kaik B, Zeidler H. A three year comparative multicenter study of auranofin and gold sodium thiomalate in the treatment of rheumatoid arthritis. Clin Rheumatol 1987;6 Suppl 2:43-52.

186. Van der Heide A, Jacobs JW, Bijlsma JW, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs: A randomized controlled trial. Ann Intern Med 1996;124:699-707.

187. Forre O. Radiologic evidence of disease modification in rheumatoid arthritis patients treated with cyclosporine: Results of a 48-week multi-center study comparing low-dose cyclosporine with placebo. Arthritis Rheum 1994;37:1506-12.

188. Van Riel PLCM, van der Heijde DMFM, Nuver-Zwart IH, van de Putte LBA. Radiographic progression in rheumatoid arthritis: Results of 3 comparative trials. J Rheumatol 1995;22:1797-9.

189. Pasero G, Priolo F, Marubini E, et al. Slow progression of joint damage in early rheumatoid arthritis treated with cyclosporin A. Arthritis Rheum 196;39:1006-15.

190. Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting anti-rheumatic therapy in rheumatoid arthritis: A 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol 1990; 17:994-1002.

191. Pincus T, Marcum SB, Callahan LF. Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second-line drugs and prednisone. J Rheumatol 1992;19:1885-94.

192. Csuka M, Carrera GF, McCarty DJ. Treatment of intractable rheumatoid arthritis with combined cyclophosphamide, azathioprine, and hydroxychloroquine. A follow-up study. JAMA 1986; 255:2315-9.

193. McCarty DJ, Harman JG, Grassanovich JL, Qian C, Klein JP. Combination drug therapy of seropositive rheumatoid arthritis. J Rheumatol 1995;22:1636-45.

194. Williams HJ, Ward JR, Reading JC, et al. Comparison of auranofin, methotrexate, and the combination of both in the treatment of rheumatoid arthritis. A controlled clinical trial. Arthritis Rheum 1992;35:259-69.

195. Wilkens RJ, Urowitz MB, Stablein DM, et al. Comparison of azathioprine, methotrexate, and the combination of both in the treatment of rheumatoid arthritis. A controlled clinical trial. Arthritis Rheum 1992;35:849-56.

196. Faarvang KL, Egsmose C, Kryger P, Podenphant J, Ingeman-Nielsen M, Hansen TM. Hydroxychloroquine and sulphasalazine alone and in combination in rheumatoid arthritis: a randomised double blind trial. Ann Rheum Dis 1993;52:711-5.

197. Porter DR, Capell HA, Hunter J. Combination therapy in rheumatoid arthritis — no benefit of addition of hydroxychloroquine to patients with a suboptimal response to intramuscular gold therapy. J Rheumatol 1993;20:645-9.

198. Haagsma CJ, van Riel PL, de Jong AJ, van de Putte LB. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol 1997; 36:1082-8.

199. Moreland LW. Inhibition of tumor necrosis factor for rheumatoid arthritis. J Rheumatol 1999;26 Suppl:7-15.

200. Moreland LW, Margolies GR, Heck LW, et al. Recombinant soluble tumor necrosis factor receptor (p80) fusion protein: Toxicity and dose finding trial in refractory rheumatoid arthritis. J Rheumatol 1996;23:1849-55.

201. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med 1997;337:141-7.

202. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. Ann Intern Med 1999;130:478-86.

203. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients in rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253-9.

204. Lovell DJ, Giannini EH, Whitmore JB, et al. Safety and efficacy of tumor necrosis factor receptor p75 fusion protein (TNFR:Fc, Enbrel™) in DMARD refractory rheumatoid arthritis [abstract]. Arthritis Rheum 1998;41 Suppl:S470.

205. Moreland LM, Cohen SB, Baumgartner S, et al. Long-term use of etanercept in patients with DMARD-refractory rheumatoid arthritis [abstract]. Arthritis Rheum 1999;42 Suppl:S-401.

206. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.

207. Elliott MJ, Maini RN, Feldmann M, et al. Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor-alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 1994;344:1105-10.

208. Elliott MJ, Maini RN, Feldmann M, et al. Repeated therapy with monoclonal antibody to tumor necrosis factor-alpha (cA2) in patients with rheumatoid arthritis. Lancet 1994;344:1125-7.

209. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor a monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552-63.

210. Elliott MJ, Maini RN, Feldmann M, et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor-alpha. Arthritis Rheum 1993;36:1681-90.

211. Boyle JA, Buchanan WW. In: Clinical rheumatology. Ch 7. London: Blackwell Scientific; 1971:167-97.

212. Duthie JJR, Thompson M, Weir MM, Fletcher WB. Medical and social aspects of the treatment of rheumatoid arthritis with special reference to factors affecting prognosis. Ann Rheum Dis 1955;14:133-49.

213. Partidge REH, Duthie JJR. A controlled trial of the effect of complete immobilization of the joint in rheumatoid arthritis. Ann Rheum Dis 1963;22:91-9.

214. Copeman WSC. Textbook of the rheumatic diseases. Ch 10. 3rd ed. E & S Livingstone; 1964:175-239.

215. Dick WC. Drug treatment of rheumatoid arthritis. In: Scott JT, editor. Copeman's textbook of the rheumatic diseases. London: Churchill Livingstone; 1978:404-46.

216. Lightfoot RW. McCarty DJ, editor. Arthritis and allied conditions. 10th ed. Baltimore: Lea & Febiger; 1985:668.

217. Joint Committee of the Medical Research Council and Nuffield Foundation. Clinical trials of cortisone, ACTH and other therapeutic measures in chronic rheumatic diseases. A comparison of prednisolone with aspirin and other analgesics in the treatment of rheumatoid arthritis. Ann Rheum Dis 1960;19:331-7.

218. Ward JR. Earlier intervention with second line therapies. J Rheumatol 1990;17 Suppl 25:18-23.

219. Kirwan JR and the Arthritis & Rheumatism Council Low Dose Glucocorticoid Study Group. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. N Eng J Med 1995;333:142-6.

220. Wassenberg S, Rau R, Zeidler H. Low dose prednisone therapy retards radiographically detectable destruction in early rheumatoid arthritis [abstract]. Arthritis Rheum 1999;42 Suppl:S243.

221. Paulus HE, Di Primeo D, Sanda M, et al. Progression of radiographic joint erosion during low-dose corticosteroid treatment of rheumatoid arthritis. J Rheumatol 2000;27:1632-7.

222. Laupacis A, Bourne R, Rorabeck C, et al. The effect of elective total hip replacement on health related quality of life. J Bone Joint Surg 1993;75A:1619-25.

223. Soderlin MK, Nieminen P, Hakala M. Functional status predicts mortality in a community based rheumatoid arthritis population.

J Rheumatol 1998;25:1895-9.
224. Pincus T, Marcum SB, Callahan LF. Long term drug therapy for RA in 7 rheumatology private practices: 2nd line drugs and prednisone. J Rheumatol 1992;19:1885-94.
225. Wolfe F. 50 years of antirheumatic therapy: the prognosis of rheumatoid arthritis. J Rheumatol 1990;17 Suppl 22:24-32.
226. Wilske KR, Healey LA. Remodelling the pyramid: a concept whose time has come. J Rheumatol 1989;16:565-7.
227. Wilske KR, Healey LA. Challenging the therapeutic pyramid: a new look at treatment strategies for rheumatoid arthritis. J Rheumatol 1990;17 Suppl 25:4-7.
228. McCarty DJ. Suppress rheumatoid inflammation early and leave the pyramid to the Egyptians. J Rheumatol 1990;17:1115-8.
229. Fries JF. Re-evaluating the therapeutic approach to rheumatoid arthritis: the "saw tooth" strategy. J Rheumatol 1990;17 Suppl 22:12-5.
230. Tugwell P, Pincus T, Yocum D, et al. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. The Methotrexate-Cyclosporine Combination Study Group. N Engl J Med 1995;333:137-41.
231. Maini R, St. Clair EW, Breedveld F, et al for the ATTRACT Study Group. Infliximab (chimeric anti-tumour necrosis factor a monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. Lancet 1999;354:1932-9.
232. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353:1568-73.
233. O'Dell JR, Haire CE, Erickson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996;334:1287-91.
234. Galindo-Rodriguez G, Avina-Zubieta JA, Fitzgerald A, et al. Variations and trends in the prescription of initial 2nd line therapy for patients with RA. J Rheumatol 1997;24:633-8.
235. Edmonds JP, Scott DC, Furst DE, Brooks P, Paulus HE. Antirheumatic drugs: a proposed new classification. Arthritis Rheum 1993;36:336-9.
236. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine in early rheumatoid arthritis. Lancet 1997;350:309-18.
237. Pincus T, O'Dell JR, Kremer JM. Combination therapy with multiple disease-modifying antirheumatic drugs in rheumatoid arthritis: a preventive strategy. Ann Intern Med 1999;131:768-74.
238. O'Dell JR, Haire C, Erikson N, et al. Efficacy of triple DMARD therapy in patients with RA with suboptimal response to methotrexate. J Rheumatol 1996;23 Suppl 44:72-4.

Evaluating Severity and Status in Rheumatoid Arthritis

FREDERICK WOLFE, JAMES R. O'DELL, ARTHUR KAVANAUGH, KENNETH WILSKE, and THEODORE PINCUS

ABSTRACT. There is general agreement regarding the most appropriate examinations and methods to use to evaluate change in status in randomized controlled trials (RCT). However, no guidelines exist to aid in determining and evaluating actual status rather than change in status, particularly when applied to individual patients with rheumatoid arthritis (RA). In addition, methods appropriate for clinical trials may not be useful in evaluating individual patients because of time constraints. This report reviews current methods of evaluation and develops modified methods, based on data bank research that will be useful in clinical practice and in the evaluation of RCT and observational studies. Using data from longitudinal observational data banks, further reduction in the number of joints examined is evaluated to reconcile the time constraints of clinical practice with the need to maintain reliability and validity. Percentile methods to determine severity status are applied to the variables used in RCT and extended further to observational studies and routine clinical practice. Shortened joint counts, based on modifications of the Ritchie method, are identified that allow for examination of groups of 18 (clinical-18) and 16 (clinical-16) joints, the clinical-16 omitting the metatarsophalangeal joints. Using percentile charts, actual severity valuations are given to the variables evaluated in the clinic as well as in RCT. Disease activity status of clinic patients can be determined quantitatively thus allowing clinicians further insight into the status and prognosis of their patients. By quantifying disease activity severity, clinicians and 3rd party payers can better evaluate the appropriateness of and response to disease modifying antirheumatic drugs and biologic therapies. Further, RCT can be evaluated as to severity status of patients participating, and the generalizability of RCT can be better evaluated. (J Rheumatol 2001;28:1453–62)

Key Indexing Terms:
DISEASE ACTIVITY
DISEASE STATUS
HEALTH ASSESSMENT QUESTIONNAIRE
RHEUMATOID ARTHRITIS
JOINT COUNTS
JOINT EXAMINATIONS

Rheumatoid arthritis (RA) is a complex disorder in which disease activity produces symptoms and damage, which in turn lead to personal and societal consequences[1-5], including work disability[1,6-13], high rates of service utilization[14-19], and premature mortality[1,20-26].

Depending on the purpose of the evaluation, one generally tries to separate the various components of illness into (1) disease activity, (2) patient symptoms and distress, (3) patient outcomes, (4) structural damage or disease outcome, and (5) societal consequences (Table 1, Figure 1). Each of these items reflects the *severity* or *status* of the patient in regard to that item. Therefore in characterizing a patient or a group of patients one may speak of radiographic severity, (severity of) disease activity, or symptom severity, for example. In addition to severity or status, a second measure of interest is the *change in severity* or *change in status*. In randomized controlled trials (RCT) the main outcome of interest is a change in status, but in observational studies (OS) actual status is most often the important outcome. In clinical care, the clinician initiates therapy on the basis of status and most often decides on the success of therapy and its continuance on the basis of status. That is, it is not the percentage of improvement that is important in the individual patient, but instead it is the actual severity level.

In RCT and OS, as well as in routine clinical care, the goal of therapy is to reduce or eliminate disease activity and symptoms. One of the difficulties in evaluating disease activity is that there are very few truly "objective" markers, of which acute phase reactants and joint swelling are the two in common use. Consequently surrogates for disease activity are utilized; the most common surrogates include pain, tender joint count, patient and physician global severity, and functional disability.

Psychosocial factors exert a strong influence on the intensity and reporting of symptoms, as well as in influencing patient outcomes. It is therefore possible to have a patient with limited disease activity who reports severe symptoms; and it is possible to have a patient with high levels of disease activity who tolerates the illness well and

From the National Data Bank for Rheumatic Diseases, Arthritis Research Center Foundation, Inc. and University of Kansas School of Medicine, Wichita, Kansas; the University of Nebraska School of Medicine, Omaha, Nebraska; University of California at San Diego, San Diego, California; Vanderbilt University, Nashville, Tennessee; and Virgina Mason Clinic, Seattle, Washington, USA.

F. Wolfe, MD, National Data Bank for Rheumatic Diseases and University of Kansas School of Medicine; J. O'Dell, MD, Professor of Medicine, University of Nebraska School of Medicine; A. Kavanaugh, MD, Associate Professor of Medicine, University of California at San Diego; T. Pincus, MD, Professor of Medicine, Vanderbilt University; K.R. Wilske, MD, Virginia Mason Clinic.

Address correspondence to Dr. F. Wolfe, Arthritis Research Center Foundation, 1035 N. Emporia, Suite 230, Wichita, KS 67214.
E-mail: fwolfe@arthritis-research.org

Docket No.: 36672.6
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ian Alexander SHIELS et. al.

Application No.: 10/531,560

Confirmation No.: 3534

Filed: 27 January 2006

Art Unit: 1654

For: TREATMENT OF OSTEOARTHRITIS

Examiner: Christina BRADLEY

DECLARATION OF RICHARD DAY PURSUANT TO 37 C.F.R. 1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

This is **Exhibit C** referred to in the Declaration of **Richard Day**.

CLINICAL ORTHOPAEDICS AND RELATED RESEARCH
Number 366, pp. 22–30

Drug Treatment for Rheumatoid Arthritis

T. Langenegger, MD; and B.A. Michel, MD

The general goals of drug treatment for patients with rheumatoid arthritis are to reduce morbidity and mortality. Because rheumatoid arthritis is a potentially devastating disease, a more aggressive treatment approach has emerged in the last decade. The modern treatment pyramid consists of nonsteroidal antiinflammatory drugs and glucocorticoids for symptomatic relief, and disease modifying antirheumatic drugs for reducing disease activity in the short term and joint damage in the long term. There is increasing evidence that a reduction of disease activity by disease modifying antirheumatic drugs alters the course of rheumatoid arthritis and that patients benefit from early installation of these compounds. The major problem with disease modifying antirheumatic drugs is their low efficacy to toxicity ratio, leading to marked reduction of the length of time a patient is taking a given drug. The new treatment strategies, including combination regimens and new drugs that are being investigated, promise better efficacy and tolerance in the near future. A step in this direction is the development of biologic agents targeting specific mechanisms in the immune response. Early results in clinical trials with antitumor necrosis factor–alpha monoclonal antibodies are encouraging.

From the Department of Rheumatology, University Hospital Zurich, Switzerland.

Reprint requests to T. Langenegger, MD, Department of Rheumatology, University Hospital Zurich, Gloriastrasse 25, 8091 Zurich, Switzerland.

List of Abbreviations Used

COX	cyclooxygenase
COX–1	cyclooxygenase 1
COX–2	cyclooxygenase 2
IL	interleukin
TGF-β	transforming growth factor beta
TNF-α	tumor necrosis factor alpha

Rheumatoid arthritis is an autoimmune disorder of unknown etiology characterized by symmetric, erosive synovitis and possible multisystem involvement.[29] The prevalence of this disease in the Western world is 1%.[29] Because there is no known cure for patients with rheumatoid arthritis and sustained spontaneous remission is rare (< 10%),[26] most patients have a chronic fluctuating disease course that if left untreated, results in progressive joint destruction, deformity, disability, and premature death.[25,29]

One study showed that patients with active, polyarticular, rheumatoid factor positive rheumatoid arthritis have a greater than 70% probability of having joint damage or erosions develop within 2 years of the onset of disease.[19] Therefore, early initiation of adequate treatment is the hallmark of treating patients with rheumatoid arthritis.[15]

The goals of treatment are to control disease activity, to reduce the probability of irreversible joint damage, to alleviate pain, to maintain function for essential activities of daily living and work, and to maximize quality of life.[55] Besides physical and occupational therapy, or-

thopaedic surgery, social work and health education, the most important part in this interdisciplinary care approach remains drug treatment.

The three major classes of drugs used in the treatment of patients with rheumatoid arthritis are the nonsteroidal antiinflammatory drugs, the glucocorticosteroids, and the disease modifying antirheumatic drugs. The authors will describe the actual aspects of these drug classes in the treatment of patients with rheumatoid arthritis, and discuss future therapeutic modalities.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Nonsteroidal antiinflammatory drugs are the principal pharmacologic agents for symptom relief in patients with rheumatoid arthritis. They act by inhibition of the enzyme COX, which is responsible for the production of the biologically active prostaglandins and thromboxanes from arachidonic acid.[60] In patients with early stage of rheumatoid arthritis nonsteroidal antiinflammatory drugs are effective in abolishing the symptoms (pain, stiffness) and signs (swelling) of acute joint inflammation. However, this is a symptomatic benefit only; the inhibition of COX is not associated with disease modifying activity, and the use of nonsteroidal antiinflammatory drugs may result in a delay of more definitive therapy.

The enzyme COX recently has been shown to have two distinct forms termed isoenzymes.[38] Cyclooxygenase–1 is responsible for the production of prostaglandins that are gastroprotective, maintain renal perfusion, and regulate platelet aggregation. Cyclooxygenase–2 produces prostaglandins found at sites of tissue inflammation. The antiinflammatory effect therefore is attributable to inhibition of COX–2. The traditional nonsteroidal antiinflammatory drugs have different selectivity to COX–1 and –2, which explains in part the different toxicity profiles. More COX–2 selective nonsteroidal antiinflammatory drugs, for example meloxicam and nabumetone, seem to show less gastrointestinal and platelet side effects.[44,64] The new highly selective COX–2 inhibitors celecoxib and rofecoxib showed in randomized controlled trials clinical efficacy similar to that of conventional nonsteroidal antiinflammatory drugs, but had far less gastrointestinal side effects and had no adverse effects on platelet function.[10,21,51]

As most patients with rheumatoid arthritis still are using the traditional nonsteroidal antiinflammatory drugs, a major issue is adverse side effects. Although nonsteroidal antiinflammatory drugs generally are well tolerated, they are associated with a spectrum of potential clinical toxicities, which varies between the different compounds. None are completely safe.[34,52] The major adverse events of nonsteroidal antiinflammatory drugs occur in the gastrointestinal tract, central nervous system, hematopoetic system, kidney, skin, liver, and on blood pressure.[48]

Gastrointestinal toxicity is clinically the most important side effect with an annual incidence of ulcers, bleeding, and perforation of 1% to 2% in patients with rheumatoid arthritis who use long term nonsteroidal antiinflammatory drugs.[50] Risk factors of these adverse events are older age, previous ulcers or bleeding, concomitant use of glucocorticosteroids and cardiovascular disease.[20,50] Prevention with misoprostol[50] or omeprazole[27] is effective in this high risk population. The better option in the future seems to be the new highly selective COX–2 inhibitors, celecoxib and rofecoxib, in patients who are at risk of having adverse events. Another major concern is nephrotoxicity. Besides interstitial nephritis, nephrotic syndrome, and end stage renal disease that occur rarely,[41,49] the most common side effect is a decrease in renal function, which is caused by a reduction in renal blood flow. Patients with impaired renal function, hypovolemia, and congestive heart failure are at risk. The role of the highly selective COX–2 inhibitors on kidney function is not yet clear. In clinical trials adverse renal effects in patients taking selective COX–2 inhibitors were similar to the adverse effects in patients who were taking conventional nonsteroidal antiin-

flammatory drugs.[10,21,51] The explanation seems to be the expression of COX–2 in the macula densa of the kidneys, and that the regulation of perfusion in the kidney is COX–1 and COX–2 dependent.[30] Hepatic injury with elevated liver enzymes is rare, reversible, and seldom fatal.[46]

GLUCOCORTICOSTEROIDS

Glucocorticosteroid use is one of the most important and controversial subjects in the treatment of patients with rheumatoid arthritis. The dramatic antiinflammatory effect of glucocorticosteroids first was described in treating patients with rheumatoid arthritis.[28] Although many major issues of glucocorticosteroid treatment remain unresolved, its local (intraarticular) and systemic use are a prominent component of rheumatologic practice because of the unsurpassed short term efficacy of these powerful drugs.[7]

Intraarticular use of glucocorticosteroids is an effective treatment of monoarticular or oligoarticular, otherwise difficult to control, synovitis.[23,35] There seems to be no increase in the rate of joint replacements in patients with frequently injected joints.[45] A period of joint rest after injection seems to be useful in extending the efficacy of glucocorticosteroids.[11]

Adverse effects of intraarticular glucocorticosteroid injections are rare and include infections (approximately 1:30,000), tendon ruptures, avascular necrosis, steroid crystal synovitis and allergic reactions. Adverse effects with frequent injections include hypercortisolism and osteoporosis attributable to the systemic effects of the steroid compound.[23]

The systemic application of glucocorticosteroids is more controversial, especially in the long term use. Short term use in dosages as much as 20 mg of prednisone for the treatment of rheumatoid arthritis flareups,[7] low dose prednisolone (7.5 mg) in patients with early stages rheumatoid arthritis for as many as 2 years,[31] induction of remission with high dose prednisone in combination with disease modifying antirheumatic drugs (methotrexate and sulfasalazine) in patients with early stages of rheumatoid arthritis, and intravenous pulse prednisolone in refractory disease all have proven to be beneficial.[5]

Long term use of glucocorticosteroids is associated with major adverse events in a dose dependent manner. Although some studies[31,43] have shown the relative safety of long term low dose glucocorticosteroids (7.5 mg prednisone or less) other studies highlight the cumulative toxicity that leads to osteoporosis, infections, peptic ulcers (in combination with nonsteroidal antiinflammatory drugs), arteriosclerosis, poorer outcome, and a shortened lifespan in patients with rheumatoid arthritis.[40,42]

If long term use of glucocorticosteroids is inevitable, osteoporosis prophylaxis is recommended by the American College of Rheumatology.[4] Preventive regimens include calcium and vitamin D,[9] although for therapy bisphosphonates such as cyclic etidronate[2] or alendronate[47] are considered.

DISEASE MODIFYING ANTIRHEUMATIC DRUGS

Disease modifying antirheumatic drugs, also called slow acting antirheumatic drugs or disease controlling antirheumatic therapeutics,[14] are substances that alter the disease course and lessen the radiologic damage. Although these drugs decrease disease activity and joint destruction in the short term, their beneficial long term effect is controversial. Only recently, epidemiologic data showed an association between consistent use of disease modifying antirheumatic drugs and improvement in long term functional outcome.[1,18]

Inflammation in patients with rheumatoid arthritis seems greatest at the onset of disease, with a maximal number of swollen joints at this time and a high probability of the patient having joint damage or erosions develop within 2 years of disease onset.[20] Other factors supporting the early use of disease modifying antirheumatic drugs include the natural sustained remission rate is low (< 10%)[26] and the nonsteroidal antiinflammatory drugs and glu-

cocorticosteroids do not seem to alter the natural course of the disease. Early and sustained use of disease modifying antirheumatic drugs is important. The concept of early intervention has been found to be beneficial in recent clinical trials[5,59] and was expressed formally in the guidelines of the American College of Rheumatology.[33]

Table 1 gives an overview of the available disease modifying antirheumatic drugs with their recommended dosage and major side effects.

Sulfasalazine and the antimalarial drug hydroxychloroquine are among the first line therapies given to patients with mild to moderate rheumatoid arthritis. Their action is associated with low toxicity and they can be combined safely with other disease modifying antirheumatic drugs.[17,39] Methotrexate and parenteral gold are the first line drugs given to patients with moderate to severe disease. Peroral gold is used rarely in Europe because of its disappointing efficacy and frequent side effect of diarrhea.

Azathioprine is used to treat patients with moderate to severe rheumatoid arthritis when the other first line drugs have failed or when there is severe extraarticular disease. Although several studies[24,65] have shown penicillamine to be an effective drug, it is not used routinely because of its slow onset of action and its high frequency of side effects. Despite studies[57,68] showing the clinical effectiveness of cyclosporin, its costs and potential of irreversible renal toxicity have limited its use in patients with severe, refractory disease or in combination with methotrexate.[58]

The alkylating drug cyclophosphamide is highly effective for treating patients with rheumatoid arthritis, but has an unacceptable high toxicity profile (oncogenicity, bladder hemorrhage, bone marrow depression, infertility). Its use is limited to patients with severe extraarticular disease (vasculitis, severe eye disease).

All the slow acting agents currently in clinical use have been shown, by short term placebo controlled randomized trials, to be more effective than placebo or equally effective to another disease modifying agent regarding inflammatory parameters and functional assessment scales. In long term use the two main problems are the relevant side effects (toxicity) and the failure to reduce disease activity under a level where additional joint destruction is unlikely (efficacy).[13] This relatively low efficacy to toxicity ratio of the available disease modifying antirheumatic drugs is the main reason that ½ of the patients take any given drug less than 2 years, except for methotrexate, which is taken continuously for more than 4 years on average.[3,12,66]

Because of problems with efficacy and toxicity associated with the use of the available disease modifying antirheumatic drugs given in single drug regimens new treatment strategies (combination therapies) and new drugs have emerged in the last years.

Combination Therapy

Combination therapy of rheumatoid arthritis has been one of the major topics in rheumatology in the last decade. Comprehensive reviews of this topic have been published by Borigini and Paulus[6] and Verhoeven et al.[61]

The rationale for combining drugs comes from the experience with combined drugs as used in oncology. Combination therapy has been used successfully in oncology with far better results in terms of efficacy and toxicity when treating patients with lymphoproliferative disease with multiple drug regimens. The theoretical arguments for combining disease modifying antirheumatic drugs in rheumatoid arthritis are the modes of action and the pharmacodynamics of the known disease modifying antirheumatic drugs differ; additive or even synergistic effects theoretically can be expected; combination therapies may allow for lower doses of individual drugs. Toxicity for individual drugs may be less severe. However, additive toxicity may be a problem; time delay can be avoided with combination regimens compared with trying single disease modifying antirheumatic drugs sequentially until an effective drug is found. Because of this delay considerable joint damage may occur; and ad-

TABLE 1. Disease Modifying Antirheumatic Drugs Used in the Treatment of Rheumatoid Arthritis

Drug	Approximate Time to Benefit (months)	Usual Maintenance Dose	Infection Ratio	Teratogenicity	Association with Cancer	Toxicity
Methotrexate	1–2	7.5–25 mg weekly (orally or intramuscularly)	moderate	strong	weak	Gastrointestinal symptoms, stomatitis, rash, alopecia, infrequent myelosuppression, hepatic toxicity and pulmonary toxicity
Sulfasalazine	1–2	2000–3000 mg daily	none	none	none	Gastrointestinal intolerance, rash, infrequent myelosuppression
Hydroxychloroquine	2–4	200–400 mg daily	none	weak	none	Rash, diarrhea, rare retinal toxicity
Gold	4–6	25–50 mg intramuscularly every 1–4 weeks, 3–6 mg orally daily	none	none	none	Rash, stomatitis, myelosuppression, thrombocytopenia (immunomediated), proteinuria
Penicillamine	3–6	250–1000 mg daily	none	moderate	none	Rash, stomatitis, dysgeusia, proteinuria, myelosuppression, autoimmune disease
Azathioprine	2–3	1.5–2.5 mg/kg/day	moderate	weak	moderate	Gastrointestinal symptoms, myelosuppression, hepatotoxicity, flulike symptoms
Cyclosporin	2–3	2.5–5 mg/kg/day	weak	none to weak	weak	Gastrointestinal symptoms, rash, flulike symptoms, tremor, hypertrichosis, hypertension, nephrotoxicity
Cyclophosphamide	2–3	1–2 mg/kg/day	strong	strong	strong	Gastrointestinal symptoms, myelosuppression, alopecia, hemorrhagic cystitis, infections, ovarian and testicular failure

dition of a second drug may prevent or delay the development of resistance to the first drug.

Successful drug combination in terms of efficacy and toxicity has been seen for several combination regimens in controlled studies: methotrexate and chloroquine,[17] methotrexate and cyclosporin,[58] methotrexate and sulfasalazine and prednisone,[5] parenteral gold and bucillamine (drug similar to penicillamine),[67] and triple therapy of methotrexate, hydroxychloroquine and sulfasalazine.[39] In addition to the better efficacy in the combination regimens in these randomized, double blind, controlled trials there were no more adverse effects in the patients receiving the combination regimens compared with those patients receiving one drug.

In the future, efforts are needed to determine the best combinations of disease modifying antirheumatic drugs, their ideal dosage, and the best application regimens (continuous combination therapy, step up disease modifying antirheumatic drugs, intermittent combination) to optimize the treatment of patients with rheumatoid arthritis.

FUTURE THERAPEUTICS

Because the goal of treating patients with rheumatoid arthritis, the induction of remission, rarely is successful with traditional disease modifying antirheumatic drugs, newer promising drugs are being investigated.

Immunosuppressants

Leflunomide inhibits pyrimidine synthesis and interferes with T and B cell function, and cytokine release and production. In randomized controlled clinical trials[36,54] the new drug shows promising efficacy.

Mycophenolate mofetil, a purine synthesis inhibitor, that is used widely in transplantation medicine, has been tested in more than 600 patients with good response and tolerance.[22]

Additional clinical trials in single drug and combination drug regimens of these immunosuppressants are ongoing in Europe and North America.

Biologic Agents

In recent years the steady increase in knowledge of mechanisms leading to tissue destruction in patients with rheumatoid arthritis and the use of the latest biotechnology techniques allowed the development of vaccination therapy or of biologic agents interfering with cell surface antigens or modulating cytokines (Table 2).[8,12,16,62] The main target of the cellular approach are T cells, which play a central role in the immune mechanism of rheumatoid arthritis. The aim of these biologic agents is to antagonize proinflammatory cytokines such as IL-1, IL-2, IL-6 and TNF-α or to stimulate or add protective cytokines such as IL-10, γ-interferon and TGF-β. Most of these compounds are in early stages of experimental animal or patient research.

Etanercept, the first available and approved biologic compound showed promising results in clinical controlled trials as monotherapy[37] or in combination with methotrexate.[63]

TABLE 2. New Strategies in Immunointervention With Biologic Agents in Rheumatoid Arthritis

Strategy	Intervention
Vaccination	T cells
	T cell receptor peptides
	HLA peptides
	antigens
T cell modulation	CD 4 mAb
	CD 5 mAb
	CD 7 mAb
	CD 7 mAb
	CDw 52 mAb
Cytokine modulation	TNF-α mAb
	soluble TNF-α receptor
	IL 1 receptor antagonist
	IL 2 mAb
	IL 6 mAb
	IL 10
	γ-interferon
	TGF-β

TNF = tumor necrosis factor; IL = interleukin, mAb = monoclonal antibody; TGF = transforming growth factor; HLA = human leucocyte antigen.

Antibiotics

The use of antibiotics in treating patients with rheumatoid arthritis is not a new approach.[53] In the last years, three double blind placebo controlled trials[32,40,56] showed significant superiority of the tetracycline antibiotic minocycline over placebo, especially in patients with early stages of rheumatoid arthritis. The mechanism of the positive effect on rheumatoid arthritis seems to be immunomodulatory or antiinflammatory or both rather than antimicrobial. Chemically derived tetracyclines, devoid of antimicrobial activity, have proven to be efficacious as well. In the future the use of minocycline may be used more often in the treatment of patients with early rheumatoid arthritis who have a mild disease course.

References

1. Abu-Shakra M, Toker R, Flusser D, et al: Clinical and radiographic outcomes of rheumatoid arthritis patients not treated with disease-modifying drugs. Arthritis Rheum 41:1190–1195, 1998.
2. Adachi JD, Bensen WG, Brown J, et al: Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. N Engl J Med 337:382–387, 1997.
3. Alarcon GS, Tracy IC, Strand GM, et al: Survival of drug discontinuation analysis in a large cohort of methotrexate treated rheumatoid arthritis patients. Ann Rheum Dis 54:708–712, 1995.
4. American College of Rheumatology Task Force on Osteoporosis Guidelines: Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 39:1791–1801, 1996.
5. Boers M, Verhoeven AC, Markusse HM, et al: Randomised comparison of combined step-down prednisone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 350:309–318, 1997.
6. Borigini MJ, Paulus HE: Combination therapy. Baillières Clin Rheumatol 9: 689–710, 1995.
7. Boumpas DT, Chrousos GP, Wilder RL, et al: Glucocorticoid therapy for immune-mediated diseases: Basic and clinical correlates. Ann Intern Med 119:1198–1208, 1993.
8. Breedveld FC: Future treatment. Baillières Clin Rheumatol 11:83–96, 1997.
9. Buckley LM, Leib ES, Cartularo KS, et al: Calcium and vitamin D3 supplementation prevents bone loss in the spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis: A randomized, double-blind, placebo-controlled trial. Ann Intern Med 125:961–968, 1996.
10. Cannon G, Caldwell J, Holt P, et al: MK-0966, a specific COX-2 inhibitor, has clinical efficacy comparable to diclofenac in the treatment of knee and hip osteoarthritis in a 26 week controlled clinical trial. Arthritis Rheum 41 (Suppl 9):196, 1998. Abstract.
11. Chakravarty K, Pharoah PDP, Scott DGI: A randomized controlled study of post-injection rest following intra-articular steroid therapy for knee synovitis. Br J Rheumatol 33:464–468, 1994.
12. Choy EH, Kingsley GH, Panayi GS: T-cell regulation. Baillières Clin Rheumatol 9:653–671, 1995.
13. De la Mata J, Blanco FJ, Gomez-Reino JJ: Survival analysis of disease modifying antirheumatic drugs in spanish rheumatoid arthritis patients. Ann Rheum Dis 54:881–885, 1995.
14. Edmonds JP, Scott DL, Furst DE et al: Antirheumatic drugs: A proposed new classification. Arthritis Rheum 36:336–339, 1993.
15. Egsmose C, Lund B, Borg G, et al: Patients with rheumatoid arthritis benefit from early second-line therapy: 5 year follow up of a prospective double blind placebo controlled study. J Rheumatol 22:2208–2213, 1995.
16. Elliott MJ, Maini RN: Anti-cytokine therapy in rheumatoid arthritis. Baillières Clin Rheumatol 9:633–652, 1995.
17. Ferraz MB, Pinheiro GR, Helfenstein M, et al: Combination therapy with methotrexate and chloroquine in rheumatoid arthritis. Scand J Rheumatol 23:231–236, 1994
18. Fries JF, Williams CA, Morfeld D, et al: Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying antirheumatic drug-based treatment strategies. Arthritis Rheum 39:616–622, 1996.
19. Fuchs HA, Kaye JJ, Callahan LF, et al: Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. J Rheumatol 16:585–591, 1989.
20. Gabriel SE, Jaakkimainen L, Bombardier C: Risk for serious gastrointestinal complications related to the use of nonsteroidal antiinflammatory drugs: A meta-analysis. Ann Intern Med 115:787–796, 1991.
21. Geis GS, Stead H, Morant S, et al: Efficacy and safety of celecoxib, a specific COX-2 inhibitor, in patients with rheumatoid arthritis. Arthritis Rheum 41 (Suppl 9): 316, 1998. Abstract.
22. Goldblum R: Therapy of rheumatoid arthritis with mycophenolate mofetil. Clin Exp Rheumatol 11 (Suppl 8):S117–S119, 1993.
23. Gray RG, Tenenbaum J, Gottlieb NL: Local corticosteroid injection treatment in rheumatic disorders. Semin Arthritis Rheum 10:231–254, 1981.
24. Hakoda M, Taniguchi A, Kamatani N, et al: Intermittent treatment with D-penicillamine is effective in lower doses with fewer adverse effects in patients with rheumatoid arthritis. J Rheumatol 21:1637–1641, 1994.
25. Harris ED: Rheumatoid arthritis: Pathophysiology and implications for therapy. N Engl J Med 322:1277–1289, 1990.
26. Harrison BJ, Symmons DPM, Brennan P, et al: Natural remission in inflammatory polyarthritis: Issues of definition and prediction. Br J Rheumatol 35:1096–1100, 1996.
27. Hawkey CJ, Karrasch JA, Szczepanski L, et al: Omeprazole compared with misoprostol for ulcers

associated with nonsteroidal antiinflammatory drugs. N Engl J Med 338:727–733, 1998.
28. Hench PS, Kendall EC, Slocumb CH, et al: The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone:compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Mayo Clin Proc 24:181–197, 1949.
29. Hochberg MC: Adult and juvenile rheumatoid arthritis: Current epidemiologic concepts. Epidemiol Rev 3:27–44, 1981.
30. Khan KN, Venturini CM, Bunch RT, et al: Interspecies differences in renal localization of cyclooxygenase isoforms: Implications in nonsteroidal antiinflammatory drug related nephrotoxicity. Toxicol Pathol 26:612–620, 1998.
31. Kirwan JR, Byron M, Dieppe P, et al: The effect of glucocorticoids on joint destruction in rheumatoid arthritis. N Engl J Med 333:142–146, 1995.
32. Kloppenburg M, Breedveld FC, Terwiel JP, et al: Minocycline in active rheumatoid arthritis. A double-blind, placebo-controlled trial. Arthritis Rheum 37:629–636, 1994.
33. Kwoh KC, Simms RW, Bloch DA, et al: Guidelines for the management of rheumatoid arthritis. Arthritis Rheum 39:713–722, 1996.
34. Langmann MJS, Weil J, Wainwright P, et al: Risk of bleeding peptic ulcers associated with individual nonsteroidal antiinflammatory drugs. Lancet 343:1075–1078, 1994.
35. McCarty DJ, Horman JG, Grassanovich JL, et al: Treatment of rheumatoid joint inflammation with intrasynovial triamcinolone hexacetonide. J Rheumatol 22:1631–1635, 1995.
36. Mladenovic V, Domlijan Z, Rozman B, et al: Safety and effectiveness of leflunomide in the treatment of patients with active rheumatoid arthritis. Arthritis Rheum 38:1595–1603, 1995.
37. Moreland LW, Baumgartner SW, Schiff MH, et al: Treatment of rheumatoid arthritis with recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med 337:141–147, 1997.
38. O'Banion MK, Sadowski HB, Winn V, et al: A serum and glucocorticoid regulated 4-kilobase mRNA encodes cyclooxygenase related protein. J Biol Biochem 266:23261–23267, 1991.
39. O'Dell JR, Haire CE, Erikson N, et al: Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 334: 1287–1291, 1996.
40. O'Dell J, Klassen LW, Haire C, et al: Treatment of early rheumatoid arthritis with minocycline or placebo. Arthritis Rheum 40:842–848, 1997.
41. Perneger TV, Whelton PK, Klag MJ: Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. N Engl J Med 331:1675–1679, 1994.
42. Pincus T, Brooks RH, Callaghan LF: Prediction of long term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. Ann Intern Med 120:26–34, 1994.
43. Reid DM, Cooper C, Kirwan JR: Effects of corticosteroids on bone mass over 2 years when used in the management of early rheumatoid arthritis. Br J Rheumatol 35 (Suppl 1): 210, 1996. Abstract.
44. Richardson C, Emery P: New cyclooxygenase and cytokine inhibitors. Baillière's Clin Rheumatol 9:731–758, 1995.
45. Roberts WN, Babcock EA, Breitbach SA, et al: Corticoid injection in rheumatoid arthritis does not increase rate of total joint arthroplasty. J Rheumatol 23:1001–1004, 1996.
46. Rodriguez LAG, Williams R, Derby LE, et al: Acute liver injury associated with nonsteroidal antiinflammatory drugs and the role of risk factors. Arch Intern Med 154:311–316, 1994.
47. Saag KG, Koehnke R, Caldwell JR, et al: Low-dose, long-term corticosteroid therapy in rheumatoid arthritis: An analysis of serious adverse events. Am J Med 96:115–123, 1994.
48. Schlegel SI: General Characteristics of Nonsteroidal Antiinflammatory Drugs. In Paulus HE, Furst DE, Dromgoole S (eds). Drugs for Rheumatic Diseases. New York, Churchill Livingstone 203–225, 1987.
49. Schlondorff D: Renal complications of nonsteroidal antiinflammatory drugs. Kidney Int 44:643–653, 1993.
50. Silverstein FE, Graham DY, Senior JR, et al: Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal antiinflammatory drugs. Ann Intern Med 123:214–249, 1995.
51. Simon LS, Lanza FL, Lipsky PE, et al: Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor. Arthritis Rheum 41:1591–1602, 1998.
52. Singh G, Ramey DR, Morfeld D, et al: Comparative toxicity of nonsteroidal antiinflammatory agents. Pharmacol Ther 62:175–191, 1994.
53. Skinner M, Cathcart ES, Mills JA, et al: Tetracycline in the treatment of rheumatoid arthritis: A double-blind controlled study. Arthritis Rheum 14:727–732, 1971.
54. Smolen JS, Kalden JR, Scott DL, et al: Efficacy and safety of Leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: A double-blind, randomised, multicentre trial. Lancet 353:259–266, 1999.
55. Stucki G, Langenegger T: Management of rheumatoid arthritis. Curr Opin Rheumatol 9:229–235, 1997.
56. Tilley BC, Alarcon GS, Heyse SP, et al: Minocycline in rheumatoid arthritis: A 48 week, double-blind, placebo-controlled trial. Ann Intern Med 122:81–89, 1995.
57. Tugwell P, Bombardier C, Gent M, et al: Low-dose cyclosporin versus placebo in patients with rheumatoid arthritis. Lancet 335:1051–1055, 1990.
58. Tugwell P, Pincus T, Yocum D, et al: Combination with cyclosporine and methotrexate in severe rheumatoid arthritis. N Engl J Med 333:137–141, 1995.
59. Van der Hejide A, Jacobs JWG, Bijlsma JWJ, et al: The effectiveness of early treatment with second line antirheumatic drugs: A randomized, controlled trial. Ann Intern Med 124:699–707, 1996.
60. Vane JR: Inhibition of prostaglandin synthesis as a mechanism of action of aspirin like drugs. Nature 231:235–237, 1971.

61. Verhoeven AC, Boers M, Tugwell P: Combination therapy in rheumatoid arthritis: Updated systematic review. Br J Rheumatol 37:612–619, 1998.
62. Wallis JW, Furst DE, Strand V, et al: Biologic agents and immunotherapy in rheumatoid arthritis. Rheum Dis Clin North Am 24:537–565, 1998.
63. Weinblatt ME, Kremer JM, Bankhurst AD, et al: A trial of etanercept, a recombinant tumor necrosis factor receptor: fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 340:253–259, 1999.
64. Wilkens RF: An overview of the long term safety experience of nabumetone. Drugs 40:34–37, 1990.
65. Williams HJ, Ward JR, Reading JC, et al: Low dose D-penicillamine therapy in rheumatoid arthritis. Arthritis Rheum 26:581–592, 1983.
66. Wolfe F: The epidemiology of drug treatment failure in rheumatoid arthritis. Baillières Clin Rheumatol 9:619–632, 1995.
67. Yasuda M, Sakai K, Oribe M, et al: Efficacy of additive DMARD therapy in patients with rheumatoid arthritis. Double-blind controlled trial using bucillamin and placebo with maintenance doses of gold sodium thiomalate. J Rheumatol 21:44–50, 1994.
68. Yocum D, Klippel JH, Wilder RL, et al: Cyclosporin A in severe, treatment refractory rheumatoid arthritis. A randomized study. Ann Intern Med 109:863–869, 1988.